Journal of Respiratory Medicine and Lung Disease

Review Article
Published: 25 Nov, 2019

Mechanisms, Diagnosis and Management of Exercise-Induced Asthma

*Nightingale Syabbalo**

Department of Medicine and Physiology, Umtata Chest Hospital, South Africa

Abstract

Exercise is one of the most common precipitants of asthma in clinical practice. In the general population the prevalence of Exercise-Induced Asthma (EIA) is reported to be 4% to 12%. The precise mechanisms for EIA are not clear, but are thought to be related to cooling and/or drying of the intrapulmunonary airways during exercise hyperpnoea. These effects may cause airway hyperosmolarity and release of inflammatory mediators from mast cells, eosinophils and basophils. Several mediators, including histamine, prostaglandins, leukotrienes and Th2 cytokines (interleukins) are known to cause airway smooth muscle contraction, microvascular leakage and oedema, and secretions. This would lead to airway narrowing and Exercise-Induced Bronchoconstriction (EIB). It has also been suggested that, both airway cooling with resultant vasoconstriction, may be followed by post-exercise rewarming hyperemia. This may result in bronchovascular engorgement and airway oedema that narrows the bronchial lumen causing symptoms of an asthmatic attack post-exercise.

Exercise spirometry is the standard method for assessing patients with exercise-induced bronchoconstriction. Non-pharmacological preventive measures include avoiding known triggers, warm-up exercises before athletic activities, and choosing sports with low level of minute ventilation. Short acting inhaled β2-adrenoceptor agonists (SABAs) have been demonstrated to be the most effective against EIA, particularly in patients with airway obstruction before exercise. In some patients, a combination of an aerosol of a β2-adrenoceptor agonist and an inhaled anticholinergic agent ora cromone. Patients with severe EIA require addition of inhaled corticosteroids (ICSs), Long-Acting β2-Adrenoceptor Agonists (LABAs), or Leukotriene Receptor Antagonists (LTRAS). LTRAs and 5-lipoxygenase inhibitors only afford partial protection against EIA when administered as monotherapy. The future of interleukin-blocking monoclonal antibodies in affording bronchoprotection against EIA is still forthcoming.

Keywords: Exercise-induced asthma; Inflammatory mediators; Exercise spirometry; Beta2-agonists; Inhaled corticosteroids

OPEN ACCESS

Correspondence:
Nightingale Syabbalo, Department of Medicine and Physiology, Umtata Chest Hospital, Umtata, Transkei, P.O. Box: 30243, Lusaka, Zambia, South Africa, Tel: +260966 486117; E-mail: nightsyab@gmail.com

Received Date: *29 Oct 2019*
Accepted Date: *18 Nov 2019*
Published Date: *25 Nov 2019*

Citation:
Syabbalo N. Mechanisms, Diagnosis and Management of Exercise-Induced Asthma. J Respir Med Lung Dis. 2019; 4(2): 1045.

ISSN: 2475-5761

Introduction

Exercise-Induced Asthma (EIA) is defined as a condition in which physical activity triggers acute airway obstruction in persons with heightened airway reactivity [1-3]. The term "thermally-induced asthma" was coined by McFadden and colleagues [2], to denote EIA, but may not be appropriate because of the multifactorial causes of Exercise-Induced Bronchoconstriction (EIB) [4]. This review discusses EIB that occurs in patients with asthma following exercise. Exercise is one of many stimuli that can induce acute episodes of airway obstruction in patients with poorly controlled asthma especially in patients with Bronchial airway Hyperresponsiveness (BHR) [1]. Apart from viral upper respiratory tract infections [5], exercise is the second most cause of an attack of asthma in children, and the presence of EIA is diagnostic of asthma. The severity of EIA indicates a lack of control of the underlying asthma. The exact mechanism(s) of exercise in causing post-exercise airway obstruction remains unclear. Current concepts of the pathophysiology of EIA revolve on airway thermodynamics during exercise [2]; changes in the osmolarity of the periciliary fluid lining the surface of the respiratory mucosa leading to release of inflammatory mediators from inflammatory cells [1]; airway rewarming-induced hyperemia and mucosal oedema; and reflex vagal bronchoconstriction [2].

The first-line treatment for EIA is Short-Acting Beta2-adrenoceptor Agonist (SABAs), and if the response to these agents is not effective a muscarinic antagonist or a chromone can be added for prophylaxis. Severe and recurrent EIA requires early use of anti-inflammatory agents such as Inhaled Corticosteroids (ICSs), or a Leukotriene Receptor Antagonists (LTRAs). Long-Acting β2-

adrenoceptor Agonists (LABAs), especially in combination with an inhaled corticosteroid are superior to either agent. The phenotypes of asthma is broadening, novel therapies for personalized therapy of EIA will probably include interleukin-blocking monoclonal antibodies. Warm-up exercises are important in attenuating EIB in both asthmatic patients and non-asthmatic individuals including elite athletes.

Epidemiology of Exercise-Induced Asthma

The prevalence of exercise-induced symptoms in asthmatics has been reported to vary in literature from 40% up to 94% in individuals with persistent asthma [1,6-8]. This wide range in the results is due to differences in the protocols used in the studies; variation in the intensity of exercise used; lack of uniformity in the methods used to detect the response, and failure to standardize the environmental conditions that control the magnitude of airway obstruction [1]. In experienced laboratories, virtually all asthmatics will demonstrate a reduction in pulmonary mechanics [1]. Airway obstruction with exertion is rarely seen in normal subjects, but it can occur in first-degree relatives of asthmatics, atopic nonasthmatic subjects; patients with cystic fibrosis; cardiac diseases, pulmonary diseases, hyperventilation syndrome [2,4], and in some patients with vocal cord dysfunction [9]. Because, EIB can occur in persons without asthma or in individuals with other cardiopulmonary diseases, many pulmonologist have advocated to use the term Exercise-Induced (EIB) in favor of EIA [4]. In the general population, the prevalence of EIB is reported to range from 14% to 12% [1]. Epidemiological studies have shown a prevalence of EIB in schoolchildren to be about 10% [7]. Exercise-induced asthma is most commonly reported among children and young adults because of their increased activity [10]. In some patients, particularly children, EIA is the only manifestation of asthma. These patients still develop EIA even while taking aerosol corticosteroids [11]. Furthermore, severe EIA can occur despite the presence of good lung function and training in asthmatics following a strenuous bout of exercise [12].

High incidence rates for EIA have been reported among highly trained athletes who participate in endurance sports that require high minute ventilation [12-15]. The epidemiology of EIA in elite athletes participating in different sports is very well summarized by the ERS and the EAACI [13], and it is reported to be as high as 90% in asthmatic elite athletes [14,15]. The prevalence rate of EIA is particularly high in endurance events such as cross country skiing [13], Olympic winter sports [14], and track and field athletes [16]. The prevalence of EIA in competitive swimmers is also high and is related to the chlorine gas and hydrochlorite in indoor swimming pools [16].

Historical Note

Exertion has been known to provoke airway obstruction in asthmatics as early as 120-200 AD, when Aretaeus the Cappadocian first reported the association between exertion and airway obstruction [17]. Late in the seventeenth century (1698), Sir John Floyer [18], an English Physician who was also an asthmatic, described the pathogenesis of exercise-induced asthma. In his publication, he noted that, exercise tasks with the highest level of minute ventilation produced the most severe symptoms. Flower's concept that, dancing is more asthmogenic than walking still holds true [18]. In 1864, Salter [19] recognized that, the exercise-induced bronchoconstriction could be accentuated if the exercise was performed in a cold environment. He also suggested that the rapid passage of fresh cold air over the bronchial mucous membrane could stimulate the airways either directly or by producing irritability of the nervous system. In 1946, Hexheimer [20] described the association between hyperventilation and EIB, utilizing objective measurement of lung function. He postulated that, hyperventilation was a key factor in induced EIB, and it was due to constrictor action of airway hypocapnia. Jones et al. [21], of Liverpool, UK, gave the first modern clinical description of exercise-induced asthma in 1962. Other mechanisms postulated in the later decades for the pathogenesis of EIA included, hyperventilation and stimulation of mechanoreceptors in the airways [22,23], hypocapnia, and lactic acidosis due to anaerobic metabolism in the exercising muscles [24].

Current Possible Underlying Mechanisms

The exact mechanism(s) of exertion in provoking post-exercise airway obstruction remains unclear. Current concepts of the pathogens of EIA revolve on airway thermodynamics during exercise [25,26]; changes in the osmolarity of the periciliary fluid lining the surface of the respiratory mucosa leading to release of inflammatory mediators [27,28]; and reflex vagal bronchoconstriction [29].

The degree of exercise-induced airway narrowing depends on the temperature and humidity of the inspired air, and on the rate of minute Ventilation (VE) achieved during exercise [25,30-35]. Prolonged running or cross-country skiing in cold dry air, for instance, is more likely to provoke exercise-induced asthma than indoor swimming [14,15]. EIA also depends on the underlying airway inflammation and hyperresponsiveness [3,36]. It is believed that, exercise initiates the endogenous release of inflammatory mediators and bronchoconstrictors, and the severity of EIA is thought to be a reflection of airway inflammation [36]. The main factor causing the mediator release is now thought to be changes in the osmolarity of periciliary fluid lining the surface of the respiratory mucosa [27,29]. Hallstrand et al. [28] demonstrated the release of the mediators such as histamine, tryptase and cysteinyl leukotrienes into sputum together with columnar epithelial cells. It is hypothesized that the biochemical events associated with regulatory changes of the inflammatory cells in response to an osmotic stimuli are associated with biochemical events that are involved in the release of mediators, and synthesis of new mediators [1,36]. The fact that cromolyn sodium, nedocromil sodium and other mast cell stabilizers attenuate EIA further supports mediator release and involvement [37].

Similarly, blockade of some of these mediators or their receptors, e.g., Leukotriene Receptor Antagonists (LTRAs) such as montelukast is used as a second-line pre-treatment for EIA [38].

Respiratory heat exchange

The development of EIA is related to the thermodynamic events that occur in the airways during exercise [31-33]. As the air flows from the nose towards the respiratory zone, heat and water are added continuously as a function of the gradient that exists between the airstream and the airways mucosa (air conditioning). During exercise there is an increase in the transfer of thermal energy from the airway mucosa to the airstream and vice versa during periods of hyperpnoea [30,33-35]. In humans, the site, magnitude and mechanisms of heat and water loss varies with breathing pattern [39]. It is also well established that higher levels of ventilation, and inspiring air with low temperature and low water content increases thermal load on the airways [33-35]. Thus, necessitating greater movement of heat and water from the mucosal surface to bring the inspired air

to body conditions of temperature and humidity. The greater the quantities of heat and water that have to be transferred, the larger the subsequent airways obstructive response, [32,33] conversely, low ventilation and inspiring air with moderate temperature and humidity minimizes the transfer, and so decrease the magnitude of EIA. However, the mechanism by which the thermal changes lead to liberation of inflammatory mediators from mast cells and eosinophils is still unsettled, but the thermal load may enhance airway epithelial dehydration. Additionally, airway cooling may stimulate parasympathetic cholinergic receptors in the airway. Stimulation of the parasympathetic nerves release acetylcholine which causes the airway smooth muscle to contract, the glandular tissue to secrete mucus, and the bronchial vasculature to dilate with increased capillary permeability. All these pathophysiological processes cause airway narrowing and symptoms of EIA [2,24].

Respiratory water loss

It was proposed by Anderson in 1985 [36] that, changes in the osmolarity of the airway mucosa due to water loss during exercise hyperpnoea is a more potent stimulus for inducing airway obstruction than heat loss. The abnormally high rate of water loss from the airways, which is required to bring large volumes of air to alveolar conditions in relative short time, leads to transient hyperosmolarity of the periciliary, paracellular and intracellular fluid [3,4,36]. The precise mechanism by which an increase in cellular osmolarity and inflammatory cells shrinkage leads to airflow obstruction remains elusive. However, it is generally believed that the osmotic changes lead to mast cells and epithelial cells degranulation, and release of a cascade of inflammatory mediators which pathophysiologically leads to bronchoconstriction. In addition, eosinophils can also be activated, producing further mediators release including eosinophil cationic proteins, leukotrienes, interleukins and reactive oxygen species (Table 1). The mediators in turn cause bronchoconstriction, mucus secretion, increased vascular permeability, and airways mucosal oedema. All these effects favor airway narrowing and precipitate the symptoms of EIA [28]. Furthermore, some of the mediators, such as histamine and prostaglandins may lead to vagal reflex bronchoconstriction, and increased microvascular leakage with resultant mucosal oedema, thus further potentiating EIB [3,29].

Rewarming-induced hyperemia

Bronchial capillary bed is hypertrophic and hyperplastic in patients with asthma compared to normal subjects. The hypothesis proposed by McFadden [2], implicating the bronchial circulation in the pathogenesis of EIB seems attractive. During exercise, there may be a transient decrease in bronchial blood flow. This may be followed by post-exercise rewarming-induced hyperemia resulting into bronchovascular engorgement and airways oedema that causes bronchial airways obstruction [2,40]. However, the precise mechanisms of post-exercise rewarming-induced hyperemia and airways oedema, are less clear. The release of vasodilatory prostaglandins and neuropeptides may modulate this vascular response [41]. Sensory neuropeptides, especially substance P and neurokinin A can lead to vasodilatation and microvascular leakage via Neurokinin (NK1)-receptors. There is overexpression of NK1 receptors in patients with exercise-induced bronchoconstriction. Neurokinin A (NKA) is a potent bronchoconstrictor, vasodilator and secretagogue in human airways [42]. NKA release can also stimulate release of the gel-forming mucin MUC5AC and increase mucus secretion during bronchospasms of EIA. It has been shown that, F-888 a novel selective NK1-receptor antagonist partially attenuates EIA [43]. Furthermore, the rewarming hyperemia may be augmented by the vasodilator effects of exhale Nitric Oxide (eNO), which is increased in asthmatic subjects who develop EIA [44].

Airway Inflammatory Mediators

Pharmacological studies have focused on the role of airway inflammatory mediators released from mast cells, eosinophils and basophils in the pathogenesis of EIA. Furthermore, bronchial biopsy specimen in one study showed mast cell degranulation 3 h after exercise in patients with EIA [45]. The reported efficacy of mast cell stabilizers, biosynthesis inhibitors, and receptor blocking drugs on attenuating EIA supports the notion that inflammatory mediators may contribute to the development of EIA [37,38]. Thus, pharmacological agents that block the activity or receptors of these mediators are useful therapies for preventing the development of EIA [38]. Nonetheless, not all the studies on EIA have demonstrated increase in mast cell-derived mediators during exercise in asthmatic patients [46]. The inflammatory mediators implicated in the pathogenesis of EIA are listed in Table 1.

Histamine

Histamine has been suggested as one of the key inflammatory mediator responsible for exercise-induced bronchoconstriction and mucosal oedema in patients with asthma. Some studies have shown that, plasma histamine levels are elevated after exercise in asthmatic patients [47-49]. Histamine released from mast cells may contribute to EIA via two mechanisms: Firstly, it has a direct bronchoconstriction effect via stimulation of H1-receptors on bronchial smooth muscles [47]. It may also stimulate airways receptors and lead to reflex vagal bronchoconstriction [29]. However, histamine action on bronchial smooth muscle and vagal stimulation contribute independently and additively in inducing EIA [29]. Secondary, histamine is a vasodilator and it may promote bronchovascular leakage, airway engorgement and oedema, and promote airway narrowing [47].

Eosinophilic cationic protein

Serum Eosinophilic Cationic Protein (ECP) levels have been

Table 1: Inflammatory mediators in exercise-induced asthma.

Histamine
Leukotrienes (LTB4, LTC4, LTD4, LTE4)
Eicocanoids (PGD2, TXB2)
Cytokines [interleukins (IL, IL-1β, IL3, IL-4, IL-5, L-12, IL-13, IL-23, IL-33)]
Thymic stromal lymphopoietin (TSLP)
Neurokinins (NK1)
Enzymes (tryptase)
Neutrophil chemotactic factor, and neutrophil myeloperoxidase
Platelet activating factor
Eosinophil-derived inflammatory mediators
Major basic protein (MBP)
Eosinophil cationic protein (ECP)
Eosinophil-derived neurotoxin (EDN)
Eosinophil-derived peroxide (EDPX)
Cytokinesinterleukin-3 (IL-3), IL-4, IL-5, IL-9,IL-13, IL-15, IL-23, IL-25, and IL-33
Reactive oxygen species

Abbreviations: IL: Interleukin; LT: Leukotriene; PG: Prostaglandins; Tx: Thromboxane

found to be elevated in subjects with EIA. There is also a correlation between pre-exercise ECP levels and the decline in Peak Expiratory Flow rate (PEF) following exercise [50]. However, the increase in ECP may reflect underlying airway inflammation and hyperresponsiveness which is common to several nonspecific stimuli, including exercise. It is also likely that other inflammatory mediators of activated eosinophils, such as leukotrienes, cytokines and reactive oxygen species are released during exercise and may be responsible for the inflammation, mucus secretion and bronchoconstriction.

Neutrophil chemotactic factor

Plasma Neutrophil Chemotactic Factor of Anaphylaxis (NCFA) was found to be increased after exercise in about 75% of asthmatics with EIA, and it has been implicated as a potential mediator for EIB [48-51]. However, both histamine and NCFA plasma levels are also raised in normal subjects, thus these changes are nonspecific [49]. An important outcome of the release of NCF is that neutrophils can be attracted to the airway mucosa and release bronchodilator mediators that could lead to attenuation of EIB or partially neutralize bronchoconstrictor mediators responsible for the late asthmatic response [3]. Similarly, Myeloperoxidase (MPO) and tryptase have been found to be elevated in athletes after heavy exercise but not after moderate training exercises. Both myeloperoxidase and tryptase are injurious to the airway epithelium and vagal receptors, and may lead to heightened airway hyperreactivity.

Leukotrienes

Activated inflammatory cells in acute asthma, such as mast cells and eosinophils are capable of generating inflammatory mediators. Among the potential mediators contributing to EIA, include Leukotrienes (LTs). Leukotrienes, particularly the sulfide peptide leukotrienes LTC4, LTD4, and LTE4 are potent bronchoconstrictors both in asthmatic and normal subjects [52]. They also promote oedema formation [53], and are secretagogues [54]. Leukotriene B4 and LTD4 are potent chemoattractants; they cause accumulation and activation of inflammatory cells, including eosinophils and neutrophils [55-57]. Interestingly, increase in urinary LTE4 and LTD4 metabolites after exercise have been reported in 3 children with asthma [58], but not in another study [59]. Recently, the role of leukotrienes in the pathogenesis of EIA has been supported based on pharmacological attenuation of EIB by leukotriene receptor antagonists [60]. An important role for LTD4 in causing EIB is suggested by the observation that a number of different LTD4-receptor antagonists have been shown to markedly reduce exercise-induces airway obstruction [60]. Furthermore, Manning et al. [60] have shown that flurbiprofen pre-treatment attenuated the development of LTD4 tachyphylaxis. This suggests that, LTD4 may be partly involved in the development exercise refractoriness, via stimulation of inhibitory prostaglandins release.

Prostaglandins

Prostaglandins D2 (PD2) and thromboxane B2 (TXB2) are very potent bronchoconstrictors and stimuli of mucus production. They initiate microvessel plasma leakage and cellular inflammation, and may play a role in airway hyperresponsiveness [61]. Urinary levels of mast cell mediator 9α,11β-prostaglandin F2 the earliest metabolite of the cell product PGD2 were found to be elevated after exercise in patients with EIA compared to control subjects [62]. This suggests that constrictor prostaglandins may play a part in the pathogenesis of EIA. Prostaglandins are also known to stimulate vagal reflexes [62]. Conversely, inhibitory prostaglandins particularly PGE2 that cause bronchial smooth muscle relaxation may play a role in modifying the bronchoconstrictor response to repeated bouts of exercise in asthmatic subjects [63]. Administration of cyclooxygenase inhibitors, such as indomethacin and flurbiprofen has been shown to attenuate exercise refractoriness in asthmatic subjects [63]. This suggests that the release of inhibitory prostaglandins is one of the possible mechanisms for affording bronchoprotection during EIB, and for affording exercise refractoriness.

Satake et al. [64] found a significant increase in PGE2 in the asthmatic patients in whom EIA did not develop, which suggests that PGE2may protect against EIA. However, the half-life of PGE2 is short and if it does provide protection against EIA it may be acting through indirect mechanisms.

Cytokinines

Several cytokines are released in asthmatic airways during airway inflammation and are responsible for migration and activation of mast cells (IL-3, IL-4, IL-9 and IL-13), and eosinophils (IL-3 and IL-5). Degranulation of eosinophils results into release of several pro-inflammatory cytokines, such as IL3, IL-5, IL-4, IL-12, IL-13, IL-23, IL-33, and Thymic Stromal Lymphopoietin (TSLP). Cytokinines cause bronchial smooth muscle contraction, microvascular leakage, airway oedema, and mucus secretion [65]. All of these pathophysiological processes may lead to airway narrowing and bronchoconstriction. A cascade of Th2 cytokines are believed to cause and orchestrate airflow limitation in asthmatic subjects, and possibly mediate the respiratory symptoms in patients who develop EIA [66]. However, there are few studies on the role of interleukins, and Interleukin Receptor Antagonists (ILRAs) on EIA. Recently, Monoclonal Antibodies (mAbs), Th2 cytokines and their receptors antagonists, and thymic stromal lymphopoietin blockers, have been targeted as an essential avenue of future research in the development of personalized therapy for severe asthma, and Th2-driven eosinophilic asthma [66].

Risk Factors

In addition to breathing cold frigid dry air and hyperventilation [3,14-16], several other factors may increase the susceptibility of an asthmatic to develop EIA. These include viral upper and lower respiratory tract infections [5], allergic rhinitis, rhinosinusitis, nasal polyposis, exposure to aeroallergens, and outdoor pollutants, e.g., smoke, sulphur dioxide, nitrogen dioxide, and ozone. The augmented obstructive response seems to be related to heightened airway hyperreactivity, and chronicity of asthma [1]. Although EIB and allergy appear to be independent traits, increased responsiveness to exercise does occur after allergen provocation in children with asthma [67]. However, vigorous exercise before antigen challenge does not increase antigen-induced bronchoconstriction. Exercise may in fact blunt the response to allergen inhalation [67].

Notably, the effect of intensive physical activity may be enhanced by the type of sports, untoward environmental conditions during activity, such as cold ambient temperature of winter sports [13-15], pollutants, allergens and organic chlorine products from indoor swimming pools in swimmers [16].

Another risk factor that may mimic EIA is exercise-induced anaphylaxis, first described by Sheffer and Austen [68]. This syndrome is clinically distinct from EIA in that it is characterized by the sensation of cutaneous warmth and pruritus followed by erythma,

Table 2: Factors that increase susceptibility of the development of exercise-induced asthma.

Exercise in a cold, and dry environment
Viral upper and lower respiratory infections
Allergic rhinitis
Rhinosinusitis
Nasal polyposis
Exposure to aeroallergens, e.g., pollen
Exercise-induced anaphylaxis, e.g., shrimp, peanut, wheat allergy
Exposure to outdoor pollutants, e.g., SO2, NO2, and ozone
Chlorine gas and hydrochlorite in swimming pools (aquatic athletes)
Medication, e.g., β-blockers, non-steroidal anti-inflammatory drugs, e.g., aspirin

urticarial, and often hypotension and upper airway obstruction following exercise [68-71]. This condition occurs together with food allergy, particularly relate to shrimp, peanuts [70-72], and wheat flour allergy [73], or salicylates prior to exercise [70,73]. Exercise-induced anaphylaxis occurs when the exercise takes place within 1-2 h after intake of the relevant food allergen [72]. Unlike exercise-induced asthma, the more significant upper airway obstruction is often more severe, with the outcome potentially fatal [70,73]. Factors that increase susceptibility of the development of exercise-induced asthma are listed in Table 2.

Clinical Features

The signs and symptoms of EIA are those of classical airway obstruction and are summarized in Table 3. They include chest tightness, dyspnea, coughing and wheezing [1,3]. Coughing may be the sole symptom in some children who develop EIA. Complaints of chest pain during or after exercise in children and adolescents may be associated with EIA. In addition, fatigue and gastrointestinal distress can occur, especially in children. Sore throat may be one of the presentations, particularly in children. Young athletes with asthma may be reluctant to admit symptoms and often present with inability to keep up with peers, despite good conditioning. Their exercise performance is poor than expected, and they may avoid athletic activities. Persons who develop EIA after exercise usually are tachypnoeic, tachycardic, and adventitious lung sounds, wheezes and rhonchi can be auscultated in the lung fields. Severe EIA is accompanied by lung hyperinflation and a reduction in arterial oxygen tension (PaO2). However, severe bronchoconstriction to warrant hospitalization is or death is exceedingly rare. With this knowledge, parents and teachers should not discourage children with asthma from participating in sports activities.

In some asthmatics, EIA can occur during exercise [1,3,4,13,36], but it is more common after cessation of exercise [3,4,58]. Thermal and mechanical inhibitions that occur during hyperventilation may account for this delay [40]. The classical symptoms and signs of bronchoconstriction usually develop 3 min to 10 min after cessation of exercise [1,3,13], and may last for 30 min or longer if left untreated. The severity of EIA depends on the underlying airway inflammation, bronchial hyperresponsiveness, duration and intensity of exercise, and level of VE achieved. EIA is worse in patients with prior severe asthma and poor lung function. Symptoms are also more marked following exercise in cold, dry environment, e.g., winter skiing in competitive athletes [14,15], pollutant and allergen exposure during exercise. Conversely, in the laboratory, humidification of inspired air attenuates the response [35]. Patients should be reassessed periodically, and if a satisfactory response is not achieved with the standard treatment and retreatment for EIA, an alternative diagnosis should be considered.

Table 3: Signs and symptoms of exercise-induced asthma.

Cough
Wheezing
Shortness of breath or dyspnoea
Chest tightness or pain
Gastrointestinal distress
Fatigue during exercise and prolonged recovery time after exercise
Poor than expected physical activities
Decreased endurance
Avoidance of physical activities or sports (primarily among young children)
Sore throat
Recurrent bronchitis, bronchiolitis or pneumonia (especially in infants and young children)

Late asthmatic response

A Late Asthmatic Response (LAR) is a second episode of airway obstruction approximately 3 h to 6 h after complete resolution of the initial bronchoconstriction [13,74-78]. LAR is characterized by a slowly developing, poorly reversible airway obstruction and inflammation [74,75]. The airway inflammation is associated with influx of eosinophils and neutrophils, and mediator release [76]. Late asthmatic responses are more frequently observed with antigen challenge later in the day [79]. In a proportion of subjects tested, the early response was followed by a LAR 6 h to 12 h after antigen challenge in 50% of the adults and 70% of the children tested [79]. LAR occurs in a few patients following EIA, and is significantly less severe than the initial response [79]. However, a late response following EIA has not been observed consistently and is a non-specific "phenomenon" that is not unique to exercise [80]. In the study of Rubinstein and colleagues [81], thirteen out of 53 patients developed a LAR, both after an exercise challenge and during a "control day" without exercise provocation. The nonreproducibility of the late phase response following EIA may reflect within-day fluctuation in airway caliber in asthmatic subjects.

Exercise refractoriness

Approximately 40% to 50% of asthmatic subjects are refractory to the effect of exercise when it is repeated within 30 min to 90 min [82,83]. There was no significant decline in the forced expiratory volume in one second (FEV_1), Peak Expiratory Flow rate (PEF), and airway resistance (Rtot) in response to repeated exercise. However, the airway response is reproducible when the challenge is repeated after an interval of 3 h to 4 h [83]. Refractoriness has been shown to be influenced by a variety of factors, such as type of exercise, severity of the initial exercise challenge, time interval between serial tests, environmental temperature and humidity (Table 3). The presence of the refractory period appears to be inversely related to the time separating the two exercise challenges, and the severity of the initial bout [80,82]. The exact mechanisms for exercise refractoriness are not well established. Several hypothesis have been proposed, including reduced responsiveness of bronchial smooth muscle; depletion of inflammatory mediators [84,85], or inhibition of mediator effects due to increased plasma catecholamine levels [86]. Exercise refractoriness may also be due to alteration in responsiveness of the bronchial

Table 4: Pharmacologic pre-treatment for prevention of exercise-induced asthma.

Inhaled β2-agonist
Short acting (salbutamol, levalbuterol, terbutaline, pirbuterol), administered 15 min before exercise
Long-acting (sameterol, formeterol), administered 30 to 60 min before exercise. Not recommended as monotherapy
Combination of LABA and inhaled corticosteroids (salmetrol and fluticasone (Advair Diskus; formetorol and budesonide (Symbicort)
Cromones
Cromlyn sodium, 5-20 mg, administered 15 to 20 min before exercise
Nedocromil sodium, 4 mg, administered 15 to 20 min before exercise
Inhaled anti-cholinergics
Ipratropium bromide, 18-36 µg puff, administered 10 min before exercise
Oxitropium, 100-200 µg puff, administered 10 min before exercise
Corticosteroids
Betamethasone dipropionate, budenoside, fluticasone, flunisolone, ciclesonide, and mometasone. Require daily administration for 2 to 4 weeks before these drugs reach their maximum bronchoprotective effects. Not recommended as monotherapy.
Oral methylxanthines
Rapid release theophyllines, 5 $mg.Kg^{-1}$, administered 1 h before exercise
Sustained release theophyllines (Theo-24, Theocron, Uniphyl), 12-20 $mg.Kg^{-1}$ daily
Leukotriene receptor antagonists
Montelukast, pranlukast, cinalukast, and zafirlukast. To be administered daily in patients who continue to exhibit symptoms despite administration of SABAs. Not recommended as monotherapy, and only recommended as step 2 treatment in patients with asthma.
5-lipoxygenase inhibitors
Zileuton
Future novel therapies
Neurokinin receptor antagonists, e.g., F888
Interleukin antibodies, e.g., IL-13 antibodies such as lebrikizumab
Interleukin receptor blockers, e.g., IL-13 and IL-4 receptors blockers such as dupilumab Interleukin receptor blockers, e.g., IL-5 receptors blockers such as mepolizumab and reslizumab
Monoclonal antibodies directed against IgE, e.g., omilizumab
Anti-TNF therapy, e.g., infliximab or etercept

microcirculation [87]. It has been shown that exercise refractoriness in asthmatic subjects can be inhibited by pre-treatment with indomethacin, this may suggest a role for inhibitory prostaglandins in the development of refractoriness [87]. The exercise refractoriness is useful because it enables athletic asthmatic subjects to participate and compete effectively in athletic activities after a warm-up session [88,89].

Investigations

Exercise spirometry is the standard method for assessing patients with exercise-induced asthma. Exercise testing is also useful for the determination of the severity of EIA, and is a helpful tool in the diagnosis and management of asthma. It is an objective method of confirming exercise-induced bronchospasm. A significant association is found between response to challenge and other measures of asthma severity [90]. Standardized protocols for exercise tests for asthmatics are available [91-94]. The American Thoracic Society (ATS) guideline recommended that an exercise load of 80% to 90% of the calculated maximum is employed in the testing of EIB with inhalation of air with a relative humidity below 50% and an ambient temperature of 22°C to 25°C while running on a treadmill for 6 min to 8 min [95]. The patient should achieve a target heart rate of 85% to 90% of the maximal heart rate [95]. At this level of exercise, ventilation is expected to reach 40% to 60% maximum ventilation. Laboratory exercise testing utilizing a treadmill or a cycle ergometer allows monitoring of the cardiopulmonary parameters throughout exercise. It is particularly useful in patients with other medical conditions and in the differential diagnosis of dyspnoea due to cardiac dysfunction from EIA [3]. A six minutes outdoor free running test is often used to evaluate EIA in epidemiological studies [90]. Free running is less stressful to children and more effective for induction of airway obstruction than treadmill running or cycling [90,91]. FEV_1 or PEF should be monitored before exercise and at 3, 5, 10, 15, 20, and 30 min after exercise. Both the American Thoracic Society and the European Respiratory Society (ERS) recommend a reduction of 10% or more in FEV_1 or PEF in the laboratory as criterion for EIB [93-95]. The percentage fall is calculated by subtracting the lowest value of FEV_1 or PEF recorded after exercise from the pre-exercise value and expressing it as a percentage of the pre-exercise value.

% Fall = Pre-exercise FEV_1- Lowest FEV_1 post-exercise × 100/ Pre-exercise FEV1

If specific conductance (Sgaw) or flow rates at 25% to 75% of the vital capacity (FEF_{25-75}) are to be used to assess EIA, a reduction of 35% or more is diagnostic [93]. It should be pointed out that, not all asthmatic subjects develop EIA during or after exercise. Therefore, a negative test does not exclude the diagnosis of EIA.

Additionally, many patients with asthma respond to the inhalation of cold, dry air with bronchoconstriction, a feature that is often used as a model of EIA [96]. Hence, bronchoprovocation with cold dry air can be used as an indirect test to diagnose EIA. Other surrogate bronchoprovocative tests include Eucapnic Voluntary

Table 5: Dosages of SABAs and LABAs used for prevention and treatment of exercise-induced asthma.

Drug	Dosage
Short-acting β2-agonist (SABAs)	
Salbutamol	50 μg per spray, two puff 15 min before exercise and as require
Levalbuterol	45 μg per spray, two puff 15 min before exercise and as require
Pirbuterol	200 μg per spray, one or two puff 15 min before exercise and as require
Long-acting (β2-agonist (LABAs)	
Salmeterol	50 μg per blister, one puff twice daily
Formoterol	12μg per capsule, one or two puff twice daily
LABAs and ICSs	
Salmeterol/fluticasone	21 μg per puff, two puffs twice daily
Formoterol/budesonide	21μg perspray, two puff twice daily

Hyperventilation (EVH) [97], hyperosmolar aerosols, such as 4.5% saline [98], adenosine monophosphate [99], and dry powder mannitol [100,101]. The Medical Commission of the Olympic Committee recommends the EVH as the current best laboratory based challenge for the identification of EIB. However, these bronchoprovocative tests require special equipment and are not tolerated and suitable to some patients, especially children. Positive histamine or methacholine challenge tests [102,103] or significant post-bronchodilator response to β2-adrenoceptor agonists, ipratropium bromide or cromolyn sodium can also aid in establishing the diagnosis. The criterion for a bronchodilator response recommended by the ERS is a 12% increase in FEV1, expressed as a per cent predicted after inhaled bronchodilator or a 200 ml increase inFEV1 [93].

Treatment

Prevention is the cornerstone of therapy for EIA and can be achieved through both pharmacological [3,104,105-108], and non-pharmacological means [4,106]. Pharmacological pre-treatment for prevention of EIA is shown in Tables 4 and 5.

Pharmacological treatment

One of the goals of asthma treatment is to enable the patient to participate in activities and exercise without limitation [1,7,13]. However, the majority of asthmatics require medications for the prevention of EIA. The underlying chronic asthma should be controlled adequately, and the dosage of the regularly prescribed anti-asthmatic medications including Inhaled Corticosteroids (ICSs) may need to be increased in patients with severe EIA [101]. Pharmacotherapy is also aimed at preventing exercise-induced bronchoconstriction and to treat the symptoms rapidly with Short Acting β2-Agonists (SABAs) when they occur [107].

Inhaled beta2-adrenoceptor agonists

Short-lived inhaled beta2-adrenoceptor agonists are the most effective and first-line pharmacological agents for prevention and treatment of EIA, particularly in patients with airflow limitation before exercise [13,101,107,108]. β2-adrenoceptor agonists are also the most potent rescue bronchodilators in patients who develop EIA. The most common prescribed SABAs and their dosage is shown in Table 5. Pre-treatment with a SABA requires the drug to be administered about 15 min before exercise, and is generally effective within 5 min to 10 min and can prevent symptoms for 2 h to 4 h. They are successful in preventing EIA in approximately 80% to 95% of the patients [3,109]. However, the bronchoprotection effects of β2-adrenoceptors agonists against EIA is usually less than 2 h [109-111], and the dosage should be repeated if another exercise session is anticipated. The duration of protection afforded by β2-adrenoceptors agonists can be increased by doubling the dose [112] or when administered in combination with cromolyn sodium [111], or ipratropium bromide [113]. The shorter duration of β2-adrenoceptors agonists in affording bronchoprotection against EIA is thought to be due to their rapid clearance from the airways by mucociliary clearance and the bronchial circulation [114].

Whilst the newer Long-Acting β2-adrenoceptors Agonists (LABAs), such as salmeterol (50 μg per blister, one or two puffs daily), or formoterol 12 μg per capsule, one or two capsule twice daily) may give up to 24-h bronchoprotection to some subjects, this is not true for all patients [115,116]. However, LABAs in combination with a controller medication can be used if SABAs do not achieve the required bronchoprotection in patients with the early and late asthmatic responses.

The reason for prolonged bronchoprotection afforded by long acting β2-adrenoceptors agonist may be related to their high lipophilicity, slower clearance, and to binding to exoreceptors in the vicinity of β2-receptors [114]. LABAs should be taken 30 min to 60 min before exercise starts. They help prevent symptoms for 10 h to 12 h [116]. Daily use of LABAs is not recommended as a monotherapy in patients with symptoms despite SABA therapy. The U.S. Food and Drug Administration has recommended that they should not be used alone in persons with severe asthma, or EIA, unless there is concomitant use of controller medication, such as inhaled corticosteroids, or inhaled cromone, or ipratropium bromide [117,118]. Similarly, the American Thoracic Society does not recommend daily use of inhaled LABAs because of the likelihood of the development of tachyphylaxis [101].

Concurrent use of inhaled LABAs and an inhaled corticosteroid (e.g., fluticasone/salmeterol (Advair Diskus), and budesonide/formoterol (Symbicort) has been shown to be effective and superior to use of inhaled corticosteroid alone [119]. Recently developed once-daily long-acting β2-agonists (e.g., indacaterol, vilanterol, olodaterol) [120-122] potentially offer better bronchodilatation properties relevant to treating severe asthma with persistent airflow obstruction, especially when combined with an ICS. Their role in bronchoprotection against EIB and LARs requires further well controlled clinical studies. Oral β2-adrenoceptors agonists or sustained release formulations are not as effective as inhaled SABAs [123]. Fugslang and associates [124], have shown that, sustained release terbutaline when given twice daily in a total dosage of 4 to 12 md/d, was unable to reduce significantly the fall in FEV1 after exercise. Oral SABAs have also an increased risk

of systemic side effects, including tremors, palpitations, tachycardia, and may be arrhythmogenic.

The other major disadvantage of β2-adrenoceptors agonists is the development of tachyphylaxis if they are taken daily for more than 4 weeks, with reduction of protective effect approximately for 2 h for SABAs and 6 h for LABAs [125-128]. The β2-adrenoceptors agonists may become less effective, and because of tolerance, EIA may have a more rapid onset and an incomplete or slower recovery of the bronchospasm [128]. The tachyphylaxis is probably due to downregulation of β2 receptors on mast cells resulting in permitting mast cells to release inflammatory mediators. After long term or regular use of β2-adrenoceptors agonists, the receptors on the mast cells may be internalized, hence, reducing the numbers of effective receptors for the agonist to function [128]. Inhaled corticosteroids do not prevent the tolerance due to β2-adrenoceptors agonists [129,130].

Actions of β2-adrenoceptors agonists

Beta2-agonists produce all their effects via the activation of surface β-receptors on the plasma membrane of many different cells [131]. Beta2-agonosts stimulation increases intracellular Cyclic Adenosine 3,5-Monophosphate (cAMP) which activates Protein Kinase A (PKA). PKA phosphorylates several proteins in the cell, and together with a decrease in cytosolic calcium ion concentration [Ca^{2+}] results in smooth muscle relaxation [132]. β2-adrenoceptors agonist also activates the maxi-K channel in the airway smooth muscle cells via the α-subunit of Gs [133]. Furthermore, β2-agonists may modulate neurotransmission in parasympathetic ganglia via an effect on preganglionin nerve endings [134]. In addition to producing bronchodilatation, β2-agonists enhance mucociliary clearance and suppress microvascular leakage from the bronchial circulation, and prevent airway oedema [134]. As a functional antagonist, they can prevent and reverse the effects of all bronchoconstrictor substances, including acetylcholine, histamine, Leukotriene (LTD4), prostaglandins, bradykinins, and endothelins [134]. Inhibition of mast cell degranulation and release of bronchoconstrictor mediators may be one of the mechanisms by which β2-agonists are bronchoprotective against EIA.

Inhaled corticosteroids

Currently, Inhaled Corticosteroids (ICSs) are considered as controller medication and the mainstay of treatment of moderate to severe asthma including persistent asthma [135]. ICSs help relieve airway narrowing and inflammation of the bronchi and bronchioles. Inhaled corticosteroids of high topical potency, such as beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide, and flunisolide are highly effective in patients with severe asthma and recurrent EIA [136,137]. Good control of asthmatic symptoms before exertion is the cornerstone for prevention of EIA; this may entail early use of inhaled corticorsteroids. The American Thoracic Society (ATS) recommends that ICSs should not only be taken before exercise but daily [101]. They should be taken for 2-4 weeks in order to achieve maximum improvement [101,107]. For instance, it has been shown that long-term inhaled steroid budesonide reduces the severity of EIA in children [137]. ICSs should not be used alone as first-line treatment of acute exercise-induced bronchospasms. The use of daily inhaled cortosteroids is recommended for patients who continue to exhibit symptoms despite administration of SABA therapy or who require daily or more frequent SABA use [101]. As a matter of caution, the use of ICSs during competitive sports is not recommended by the Medical Commission of the International Olympic Committee (IOC), World Anti-Doping Association (WADA), and other International Sports Organizations [138-140].

Mast cell stabilizing agents

Mast cell stabilizing agents such as cromolyn sodium and nedocromil sodium are effective in preventing EIA, with a success rate of about 70% to 85% [141-143]. However, they are less effective than SABAs [143], and are recommended as a second-line treatment. They can be given in combination with SABAs in patients with moderate to severe asthma, and they have a synergistic effect [111]. They are given 15 min to 20 min before exercise, and their duration of action is short about 1 h to 2 h. They can also be used to prevent the late response to exercise [3].

Anticholinergic agents

There has been important advancement in muscarinic pharmacology with genetically sequencing of five subtypes of muscarinic receptors (M1-M5) in the airways, which appear to serve different physiological functions [144]. M1 receptors are facilitatory at nicotinic receptors and may be involved in "setting" the efficiency of ganglionic transmission [144]. Blockade of M1 receptors result in reduced reflex bronchoconstriction. The bronchoconstrictor action of acetylcholine in human airways is mediated entirely via M3 receptors. By contrast, M2 receptors located at cholinergic nerve terminals inhibit release of acetylcholine, thus acting as autoreceptors. Although vagal stimulation of bronchial smooth muscles has been implicated in the pathogenesis of EIA, anticholinergic drugs have a modest inhibitory effect on EIA [145]. For example, ipratropium bromide although it is a potent muscarinic receptor antagonist, it only partially inhibits EIA. Furthermore, its effects are rather variable, and it should not be used as monotherapy for prevention of EIA. However, a combination of ipratropium bromide and a β2-agonists may be effective in some patients with severe EIA [111]. Another major problem with most anticholinergic agents is that, they have a short duration of action (1 h), and the dosages may need to be repeated. Recently, several different subtypes of muscarinic receptors have been distinguished, raising the possibility of developing more selective and Long-acting Anti-Muscarinic Agents (LAMAs), such as oxitropium bromide and tiotropium bromide [128,146]. The role of LAMAs and other newer anticholinergic drugs such as aclidinium bromide and glycopyrronium in prophylaxis against EIA remains to be established.

Xanthine derivatives

Xanthine derivatives such as theophylline are third-line treatment and are rarely required or suggested except if there is failure of bronchoprotection with SABAs and ICSs. However, xanthines have impressive mechanisms of action, and possibly by the development of new agents, they may have a role in the prevention of EIA. Pharmacologic actions of theophylline include bronchodilatation, anti-inflammatory, immunomodulation, and enhancement of mucociliary clearance. One mechanism by which theophylline produce bronchodilatation is by inhibiting Phosphodiesterase (PDE) [147,148]. Phosphodiesterase breaks down cyclic Adenosine Monophosphatase (cAMP) in the cell, thereby leading to a decrease in intracellular cAMP. Theophyllines antagonize this effect and maintain levels of cAMP and thus relaxes bronchial smooth muscles [148]. Nonetheless, methylxanthines are less effective bronchodilators and require to be taken orally daily.

Another pharmacological action of theophylline is that it is a potent inhibitors of adenosine at therapeutic concentration. Inhaled adenosine causes bronchoconstriction in asthmatics via release of histamine from mast cells. This effect is blocked by theophylline [149]. Unfortunately, adenosine antagonism may be responsible for some of the side effects of theophylline, such as cardiac arrhythmias, central nervous system stimulation, and diuresis.

The PDE superfamily comprise of seven distinct isoenzyme families which have been distinguished based on substrate specificity and the development of selective inhibitors [150]. Isoform-selective inhibitors are available for most PDE families, e.g., enprofylline. Most are substrate-site-derived inhibitors, but few act at allosteric sites [150,151]. In general, these compounds are at least 30-fold selective for the PDE against which they are targeted [152]. Some PDE isoenzymes (PDE3, PDE4, and PDE5) may be more specific to airway smooth muscle, and offer opportunity for the treatment of asthma [153], and EIA. Additionally, second generation PDE4 inhibitors have a notably appealing therapeutic profile [150,152]. They have a broad anti-inflammatory activity coupled with additional bronchodilatatory and neuromodulatory actions, for example, PDE3 inhibitors attenuates bronchial smooth muscle contraction and bronchospasm [153]. Roflumilast a phosphodiesterase 4 inhibitor has been reported to attenuate mild EIB [154]. These newer agents probably will have a role in affording bronchoprotection in patients with asthma and EIA, or in preventing the late asthma responses.

Leukotriene receptor antagonists

The cysteinyl leukotrienes, LTC4, LTD4, and LTE4 are potent bronchoconstrictors that may play a role in the pathogenesis of EIA. Several Leukotriene Receptor Antagonists (LTRAs), and LT biosynthesis inhibitors, such as cinalukast [155], zileuton [156], and montelukast [157-161], have been shown to partially reduce the severity of EIA. This lends support that arachidonic metabolites are released during exercise, and in part play a role in EIA. However, all of the above studies have shown residual bronchoconstriction, which probably indicates other mediators in the pathogenesis of EIA [156-159]. For example, zileuton (600 mg) administration orally 2 h prior to exercise resulted in 28% reduction in FEV_1, *vs.* 16% fall seen in patients receiving placebo [156]. The degree of bronchoprotection afforded by LT antagonists is comparable to that afforded by mast cell stabilizing agents, such as cromolyn and nedocromil, but less than that due to SABAs [159]. Another disadvantage with long-term treatment with some of the LTD4 antagonists, for example, cinalukast (10 mg/d) is that they cause loss of protection against EIA after some time. The reasons for loss of protection are less clear [155]. However, montelukast (Singulair) given as a single 10 mg dose, has been shown to have an onset of action within two hours and continuous EIB protection at 2 h and eight and one-half hours, in comparison with salmeterol; and montelukast is more effective at 24 h [159,161]. It is reported to reduce the percentage fall in FEV1 by 40% to 60%, and reduce the recovery time of FEV1, but is not as effective as a short-acting β2-agonist in preventing bronchoconstriction. Montelukast has also not been shown to cause tachyphylaxis [157]. LTRAs should not be used as monotherapy for prevention of EIA. They should be administered as second-line treatment in combination with SABAs or ICSs in patients with mild to moderate EIA. The leukotriene receptor antagonists seem to be more favourable as add-on therapy in patients with both allergic rhinitis and EIA.

Antihistamines

Terfenadine is a selective and potent H1-receptor antagonist. Terfenadine pretreatment partially inhibits EIA when administered orally (180 mg), 2 h to 3 h before exercise [162,163]. Although histamine plays an important role in EIA, the therapeutic advantage of bronchoprotection afforded by antihistamines is limited. Prevailing evidence suggests antihistamines used in the treatment of allergic rhinitis and asthma might not be bronchoprotective in attenuating EIA [164]. Therefore, antihistamines including the third generation H1-blockers alone or in combination with LTRAs are rarely used as prophylaxis for EIA.

Loop Diuretics

Inhaled furosemide, an inhibitor of Na-K-Cl co-transporter has been shown to partially inhibit EIA in asthmatic subjects when given as an aerosol [165-167]. The changes in osmotic and ionic epithelial environment due to furosemide probably dampen the responsiveness of sensory receptors, and thus inhibit the vagally mediated component of EIA [126]. It has been suggested that furosemide may have a mast cell stabilizing effect [165-167], and probably inhibits airway postganglionic cholinergic fibers. It may also attenuate EIA by attenuation of intra-airway thermal gradient [124]. Release of inflammatory mediators which relaxes bronchial smooth muscle may partly be one of the mechanisms of action of furosemide. Prostaglandin E2, is an inhibitory prostanoid that has been shown to attenuate EIA, it has considerable bronchoprotective effects in patients with asthma [165-167]. The bronchodilator effect of furosemide 300 mg given by a jet nebulizer is comparable to 4 mg of nedocromil given by a metered dose inhaler or disodium cromoglycate in children with EIA [126,128]. The combination of these treatments induces additive effects [165-167]. However, in clinical setting, loop diuretics are rarely used for treatment of asthma. Similarly, although low-molecular weight heparin has been shown to attenuate EIB in few studies [168], there are *priori* effective and safe drugs to prevent and treat EIA.

Novel therapies for exercise-induced asthma

Activated eosinophils in the airways play an important role in the development of eosinophilic asthma by releasing Th2 inflammatory mediators and bronchoconstrictors such as cytokines (e.g., interleukins) [169,170]. There are very few studies which have investigated the role of monoclonal antibodies and interleukin blockers in bronchoprotection against EIA. Recently, it has been shown that there is an association between exercise-induced respiratory symptoms and Th2 cytokines [171,172]. Future therapies for severe asthma and prophylaxis of EIA will include Th2 oriented therapies using monoclonal antibodies and interleukin receptor antagonists. Lebrikizumab (IL-13 blocking monoclonal antibody), and dupilumab (IL-4 receptor α blocking monoclonal antibody) have been shown to improve lung function in asthmatics with high levels of periostin [173], and in patients with lower asthma severity [174], respectively. They have also been shown to reduce the rate of exacerbations of asthma. Mepolizumab (IL-5 antagonist) has also been shown to improve airflow limitation in patients with severe eosinophilic-driven asthma phenotype [175,176], and has a glucocorticoid-sparing effect in patients with eosinophilic asthma [177]. The recently approved interleukin-5 antagonist reslizumab, has been shown be safe and efficient in the treatment of severe and poorly controlled eosinophilic asthma, and to reduce exacerbation [178-181].

Unfortunately, serious treatment-related anaphylactic reactions can occur in about 0.3% of reslizumab recipients [182], which require the patients to be monitored during and for an appropriate period after treatment [183]. These novel therapies appeal promising as add-on treatment for severe asthma, eosinophilic asthma, exercise-induced asthma, and probably late asthmatic responses. Their steroid-sparing effect would be an advantage in the pre-treatment of patients with severe and recurrent EIA who require oral corticosteroids, because of the adverse effects of steroids.

Non-pharmacological treatment

Non-pharmacological treatment for exercise-induced asthma include advising the subject to avoid exercise in cold, foggy and dry environment, and to wear a heat exchanger mask when exercising in cold [184], or polluted environment [4,13,101,106]. Similarly, prolonged exercise in the heat should be avoided. Individuals who experience EIB should choose a sport with low levels of ventilation to avoid exercise hyperpnoea which may trigger bronchoconstriction. Patients who are allergic to pollen aeroallergens should not undergo strenuous exercise outdoors during high pollen season. The American Thoracic Society recommends interval or combination of warm-up exercise before planned exercise for all patients with exercise-induced bronchoconstriction [101]. Exercise conditioning includes warm-up exercise performed 45 min to 60 min before a workout or competition. The warm-up should be 10 min to 15 min with an objective of reaching 50% to 60% of maximum heart rate [13,101,106]. At this level of exercise, ventilation is expected to reach at 40% to 60% maximum. This is helpful because of exercise refractoriness following warm-ups. The abrupt onset and sudden cessation of exercise puts persons more at risk of developing EIA. A cool-down lasting for 5 min to 10 min at the end of exercise is beneficial because it minimizes sudden decline in cardiopulmonary function. It may also prevent rapid rewarming that could lead to bronchovascular engorgement, airway oedema and bronchoconstriction. Dietary supplement with fish oil (omega-3 fatty acids) and ascorbic acid, and a low sodium intake has been suggested to prevent EIB [185], but appears to be inconclusive in attenuating EIB [140].

Physical conditioning increases the ability to work at lower levels of ventilation. Several cardiopulmonary programs have been recommended for asthmatics [186,187]. Although these aerobic programs do not change bronchial hyperresponsiveness, regular exercise may attenuate exercise-induced decline in FEV1 and PEF. They also improve self-confidence and physical fitness; reduce the frequency of the attacks, and regular use of rescue bronchodilators, and school absenteeism.

Prophylaxis and treatment of EIA in elite athletes

The prevalence of asthma and bronchial hyperresponsiveness is markedly increased in elite athletes, especially with endurance sports, prolonged sports, and winter Olympic sports. The drugs used for pretreatment, and treatment of EIA are the same as those used in non-asthmatic subjects (Table 4 and 5). In athletes with documented EIB, it is best to start with a short acting β2-agonist as pre-treatment, and if the bronchoconstriction is not relieved a second-line drugs can be added. These include mast cell stabilizers, leukotriene receptor antagonists, and inhaled corticosteroid, or substitution of the SABA by a LABA. When prescribing medication for high-level athletes, physicians should be aware of which drugs require waiving by the specific organization for that particular sport, e.g., WADA, FIFA, or IOC. A comprehensive list of the prohibited drugs for competitive athletes is found in references [138-140], and a list of the prohibited drugs is usually updated annually and can be found on the WADA web site [138]. A matter of interest is that, 61% of the 1984 United States Olympic team members with EIA won an Olympic medal.

Conclusion

The precise mechanism(s) of EIA are not yet certain, but are likely to be due to cooling and/drying of the intrapulmonary airways leading to hyperosmolarity of periciliary fluid lining the surface of the respiratory mucosa, and post-exercise rewarming hyperemia. This in turn causes release of inflammatory mediators from inflammatory cells, which leads to airway smooth muscle contraction, microvascular leakage, oedema, and bronchoconstriction. Short acting β2-inhaled agonists are the most effective and mainstay of prevention and treatment of EIA, particularly in patients with airflow limitation before exercise. A combination therapy with inhaled corticosteroid with LABA, or with LTRA is recommended in patients with severe symptoms of EIA. Monoclonal antibodies and interleukin receptor blockers are important target for novel anti-asthma drugs, which could be useful as prophylaxis for EIA. Interval warm-up exercises before competitive sports may be helpful in preventing EIB.

References

1. Anderson SD. Exercise-induced asthma. In Middleton E, Reed C, Ellis E, Adkinson NF, Yunginger JW, editors. Allergy: Principles and Practice. 3rd ed. St Louis, CV Mosby Company. 1988;2:1156-75.
2. McFadden ER. Exercise-induced airway obstruction. Clin Chest Med. 1995;16(4):671-82.
3. Weiler JM, Anderson SD, Randolph C, Bonini S, Craig TJ, Pearlman DS, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. Am Allergy Asthma Immunol. 2010;105(6 Suppl):1-47.
4. Randolph C. An update on exercise-induced bronchoconstriction with and without asthma. Curr Allergy Asthma Rep. 2009;9(6):433-8.
5. Heir T, Larssen S. The influence of training intensity, airway infections and environmental conditions in bronchial responsiveness in cross-country skiers. Scan J Med Sci Sports. 1995;5(3):152-9.
6. McFadden ER, Kenner KAM, Strol KP. Postexercise airway rewarming and thermally-induced asthma. J Clin Invest. 1986;78(1):18-25.
7. Jones RS, Buston MH, Wharton MJ. The effect of exercise on ventilatory function in the child with asthma. Br J Dis Chest. 1962;56:78-86.
8. Randolph C. Paediatric exercise-induced bronchoconstriction. Contemporary development in epidemiology, pathogenesis, presentation, diagnosis, and therapy. Curr Allergy Asthma Rep. 2013;13(6):301-5.
9. McFadden RJ, Zawadski DK. Vocal cord dysfunction masquerading as exercise-induced asthma. A physiologic cause of "choking" during asthmatic activities. Am J Respir Crit Care Med. 1996;153(3):942-7.
10. Anderson SD. Issues in exercise-induced asthma. J Allergy Clin Immunol. 1985;76(6):763-72.
11. Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. Arch Dis Child. 1989;64(10):1452-6.
12. Carlsen KA, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: Part 1 of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. Allergy. 2008;63(4):387-403.

13. Larsson K, Ohlsén P, Larsson L, Malmberg P, Rydström PO, Ulriksen H. High prevalence of asthma in cross country skiers. BMJ. 1993;307(6915):1326-9.

14. Wilber RL, Rundell KW, Szmedra Im J, Drake SD. Incidence of exercise-induced bronchoconstriction in Olympic winter sports athletes. Med Sci Sports Exerc. 2003;32(4):732-7.

15. Schoene RB, Giboney K, Schimmel C, Hagen J, Robinson J, Schoene RB, et al. Spirometry and airway reactivity in elite track and field athletes. Clin J Sport Med. 1997;7(4):257-61.

16. Barnard A, Carbonnelle S, Michel O, Hiuet S, De Burbure C, Buchet JP, et al. Lung permeability and asthma prevalence in school children: unexpected association with attendance at indoor chlorinated swimming pools. Occup Environ Med. 2003;60(6):385-94.

17. Adams F. The exact work of Aretaeus of Cappadocian. London, Sydenham Society. 1856;316.

18. Flower J. A treatise of asthma. 1698;39:17-8.

19. Salter HH. On asthma: Its pathology and treatment. Philadelphia: Blanchard and Lea. 1864;132-153.

20. Herxheimer H. Hyperventilation asthma. Lancet. 1946;1(6386):83-7.

21. Jones RS, Buston MH, Wharton MJ. The effect of exercise on ventilatory function in the child with asthma. Br J Dis Chest. 1962;56:78-86.

22. Crompton GK. An unusual example of exercise-induced asthma. Thorax. 1968;23(2):165-7.

23. Ferguson A, Addington WW, Gaensler EA. Dyspnea and bronchospasm from inappropriate postexercise hyperventilation. Ann Intern Med. 1969;71(6):1063-72.

24. Vassallo CL, Gee JBL, Domm BM. Exercise-induced asthma: Observations regarding hypocapnia and acidosis. Am Rev Respir Dis. 1972;105(1):42-9.

25. Bar-Or O, Neuman I, Dotan R. Effects of dry and humid climates on exercise-induced asthma in children and preadolescents. J Allergy Clin Immunol. 1977;60(3):163-8.

26. Deal EC, McFadden ER, Ingram RH, Strauss RH, Jaeger JJ. Role of respiratory heat exchange in production of exercise-induced asthma. J Appl Physiol Respir Environ Exerc Physiol. 1979;46(3):467-75.

27. Anderson SD, Rodwell LT, Daviskas E, Spring JF, Du Toit J. The protective effect of nedocromil sodium and other drugs on airway narrowing provoked by hyperosmolar stimuli: A role of airway epithelium. J Allergy Clin Immunol. 1996;2:S124-S34.

28. Hallstrand TS, Moody MW, Wurfel MM, Schwartz LB, Henderson WR Jr, Aitken ML. Inflammatory basis of exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2005;172(6):679-86.

29. Finnerty JP, Holgate ST. The contribution of histamine release and vagal reflexes, alone and in combination, to exercise-induced asthma. Eur Respir J. 1993;6(8):1132-7.

30. Gilbert IA, Fouke JM, McFadden ER Jr. Heat and water flux in the intrathoracic airways and exercise-induced asthma. J Appl Physiol (1985). 1987;63(4):1681-91.

31. McFadden ER. Exercise-induced asthma: assessment of current etiologic concepts. Chest. 1987;91(Suppl 6):151S-157S.

32. Chen WY, Horton DJ. Heat and water loss from the airways and exercise-induced asthma. Respiration. 1977;34(6):305-13.

33. Strauss RH, McFadden ER, Ingram RH, Jaeger JJ. Hyperpnea and heat influx: initial reaction sequence in exercise-induced asthma. J Appl Physiol Respir Physiol. 1979;46(3):476-83.

34. Strauss RH, McFadden ER Jr, Ingram RH Jr, Jaeger JJ. Enhancement of exercise-induced asthma by cold air. N Engl J Med. 1977;297(14):743-7.

35. Bundgaard A, Ingemann-Hansen T, Schmidt A, Halkjaer-Kristensen J. Influence of temperature and relative humidity of inhaled gas on exercise-induced asthma. Eur J Respir Dis. 1982;63(3):239-44.

36. Anderson SD. Exercise-induced asthma: the state of the art. Chest. 1985;87(5):191S-195S.

37. Spooner CH, Spooner GR, Rowe BH. Mast cell stabilizing agents to prevent exercise-induced bronchoconstriction. Cochrane Database Syst Rev. 2003;(4)CD002307.

38. Coreno A, Skowronski M, Kotaruc C, McFadden ER. Comparative effects of long-acting beta2-agonist, leukotriene receptor antagonist, and 5-lipoxygenase inhibitor on exercise-induced asthma. J Allergy Clin Immunol. 2000;106(3):500-6.

39. Solway J, Pichurko BM, Ingenito EP, McFadden ER Jr, Fanta CH, Ingram RH Jr, et al. Breathing pattern affects airway wall temperature during cold air hyperpnea in humans. Am Rev Respir Dis. 1985;132(4):853-7.

40. McFadden ER. Hypothesis: exercise-induced asthma as a vascular phenomenon. Lancet. 1990;335:880-3.

41. Baile EM, Godden DJ, Paré PD. Mechanism for increase in tracheobronchial blood flow induced by hyperventilation of dry air in dogs. J Appl Physiol (1985). 1990;68(1):105-12.

42. Barnes PJ, Baraniuk JN, Belvisi MG. Neuropeptides in the respiratory tract. Part I. Am Rev Respir Dis. 1991;144(5):1187-98.

43. Chinose M, Miura M, Yamauchi H, Kagemaya N, Tomaki M. A neurokinin 1-receptor antagonist improves exercise-induced airway narrowing in asthmatic patients. Am Rev Respir Crit Care Med. 1996;153(3):936-41.

44. Linkosalo L, Lehtimäki L, Holm K, Kaila M, Moilanen E. Relation of bronchial and alveolar nitric oxide to exercise-induced bronchoconstriction in atopic children and adolescents. Pediatr Allergy Immunol. 2012;23(2):360-6.

45. Crimi E, Balbo A, Milanese M, Miadonna A, Rossi GA, Brusasco V. Airway inflammation and occurrence of delayed bronchoconstriction in exercise-induced asthma. Am Rev Respir Dis. 1992;146(2):507-12.

46. Jarjour NN, Calhoun WJ. Exercise-induced asthma is not associated with mast cell activation or airway inflammation. J Allergy Clin Immunol. 1992;89(1 Pt 1):60-8.

47. Barnes PJ, Brown MJ. Venous plasma histamine in exercise- and hyperventilation-induced asthma in man. Clin Sci. 1981;61(2):159-62.

48. Lee TH, Brown MJ, Nagy L, Causon R, Walport MJ, Kay AB. Exercise-induced release of histamine and neutrophil chemotactic factor in atopic asthmatics. J Allergy Clin Immunol. 1982;70(2):73-81.

49. Belcher NG, Murdoch R, Dalton N, Clark TJH, Rees PJ, Lee TH. Circulating concentrations of histamine, neutrophil chemotactic activity, and catecholamines during the refractory period in exercise-induced asthma. J Allergy Clin Imunol. 1988;81(1):100-10.

50. Lee TH, Nagakura T, Papageorgiou N, Cromwell O, Iikura Y, Kay AB. Mediators in exercise-induced asthma. J Allergy Clin Immunol. 1984;73(5 Pt 2):634-9.

51. Venge P, Henriksen J, Dahl R, Håkansson L. Exercise-induced asthma and the generation of neutrophil chemotactic activity. J Allergy Clin Immunol. 1990;85(2):498-704.

52. Hallstrand TS, Henderson WR. Role of leukotienes in exercise-induced bronchoconstriction. Curr Allergy Asthma Rep. 2009;9(1):18-25.

53. Barnes NC, Piper PJ, Costello JF. Comparative effects of inhaled leukotriene C4, leukptriene D4 and histamine in normal human subjects. Thorax. 1984;39:500-01.

54. Dahlen SE, Bjork T, Hedqvist P, Arfors KE, Hammarström S, Lindgren JA, et al. Leukotriene promote plasma leakage and leukocyte adhesion in post-capillary vessels. *In vivo* effects with relevance to acute inflammatory response. Proc Nat Acad Sci. 1981;78(6):3887-91.

55. Coles ST, Neill KM, Reid LM, Austen KF, Nii Y, Corey EJ, et al. Effects of leukotrienes C4 and D4 on glycoproteins and lysosome secretion by human bronchial mucosa. Prostaglandins. 1983;25(2):155-170.

56. Smith MJM, Ford-Hutchinson AW, Bray MA. Leukotriene B: potential mediator of inflammation. J Pharmacol. 1980;32(7):51-78.

57. Lewis RA, Austen KF, Soberman RJ. Leukotriene and other products of 5-lipoxygenase pathway: biochemistry and relation to pathobiology in human diseases. N Eng J Med. 1990;323(10):645-55.

58. Kikawa Y, Miyanomae T, Inoue Y, Saito M, Kakai I, Shigematsu Y, et al. Urinary leukotriene E4 after exercise challenge in children with asthma. J Allergy Clin Immunol. 1992;89(6):1111-19.

59. Taylor IK, Wellings R, Taylor GW, Fuller RW. Urinary leukotriene E4 secretion in exercise-induced bronchoconstriction. Am Rev Respir Dis. 1992;145(4 part 2):A15.

60. Manning PJ, Watson RM, Margolskee DJ, Williams VC, Schwartz JL, O'Byrne PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D4 receptor antagonist. N Engl J Med. 1990;323(25):1736-9.

61. O'Sullivan S, Rouquet A, Dahlén B, Larsen F, Eklund A, Kumlin M, et al. Evidence for mast cell activation during exercise-induced bronchoconstriction. Eur Respir J. 1998;12(2):345-50.

62. Beasley R, Varley J, Robinson C, Holgate ST. Cholinergic-mediated bronchoconstriction induced by prostaglandin D2, its metabolite 9a, 11ß-PGF2, and PGF2a in asthma. Am Rev Respir Dis. 1987;136(5):1140-4.

63. O'Byrne PM, Jones GL. The effect of indomethacin on exercise-induced bronchoconstriction and refractoriness after exercise. Am Rev Respir Dis. 1986;134(1):69-72.

64. Sakate T, Kato M, Tagaki K. Role of prostaglandins in exercise-induced asthma. Adv Physiol Sci. 1981;10:369-77.

65. Kuperman DA, Huang X, Koth LL, Chang GH, Dolganov GM, Zhu Z, et al. Direct effect of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. Nat Med. 2002;8(8):885-9.

66. Kuchar E, Miskiewicz K, Nitsch-Osuch A, Kurpas D, Han S, Szenborn L. Immunopathology of exercise-induced bronchoconstriction in athletes--a new modified inflammatory hypothesis. Respir Physiol Neurobiol. 2013;187(1):82-7.

67. Mussaffi H, Springer C, Godfrey S. Increased bronchial responsiveness to exercise and histamine after allergen challenge in children with asthma. J Allergy Clin Immunol. 1986;77(1 Pt 1):48-52.

68. Sheffer AL, Austen KF. Exercise-induced anaphylaxis. J Allergy Clin Immunol. 1980;66(2):106-11.

69. Buchbinder EM, Bloch KJ, Moss J, Guiney TE. Food-dependent, exercise-induced anaphylaxis. JAMA. 1983;250(21):2973-4.

70. Kidd JM, Cohen SH, Sosman AJ, Fink JN. Food-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol. 1983;71(4):407-11.

71. Casale TB, Keahay TM, Kalinger M. Exercise induced anaphylaxis: Insights into diagnostic and pathophysiologic features. JAMA. 1986;255(15):2049-53.

72. McNeil D, Strauss RH. Exercise-induced anaphylaxis related to food intake. Ann Allergy. 1988;61(6):440-2.

73. Gall H, Steinert M, Peter RU. Exercise-induced anaphylaxis to wheat flour. Allergy. 2000;55(11):1096-7.

74. Bierman CW, Spiro SG, Petheram I. Characterization of the late response in exercise-induced asthma. J Allergy Clin Immunol. 1984;74(5):701-6.

75. Zawadski DK, Lenner KA, McFadden ER. Re-examination of the late asthmatic response to exercise. Am Rev Respir Dis. 1988;137(4):837-41.

76. Lee TH, Nagakura T, Papageorgiou N, Iikura Y, Kay AB. Exercise-induced late asthmatic reactions with neutrophil chemotactic activity. N Engl J Med. 1983;308(25):1502-5.

77. Horn CR, Jones RM, Lee D, Brennan SR. Late response in exercise-induced asthma. Clin Allergy. 1984;14(4):307-9.

78. Iikura Y, Nagakuwa T, Lee TH. Factors predisposing to exercise-induced late asthmatic responses. J Allergy Clin Immunol. 1985;75(2):285.

79. Metzger WJ, Richardson HB, Worden K, Monick M, Hunningake DW. Bronchoalveolar lavage of allergic asthmatic patients following allergen bronchoprovocation. Chest. 1986;89(4):477-83.

80. Durham SR. Late asthmatic responses. Respir Med. 1990;84(4):263-8.

81. Rubinstein I, Levinson H, Slutsky AS, Hak H, Wells J, Zamel N, et al. Immediate and delayed bronchoconstriction after exercise in patients with asthma. N Engl J Med. 1987;317(8):482-5.

82. Nowak D, Kuziek G, Jörres R, Magnussen H. Comparison of refractoriness after exercise- and hyperventilation-induced asthma. Lung. 1991;169(2):57-67.

83. Edmunds AT, Tooley M, Godfrey S. The refractory period after exercise induced asthma: its duration and relationship to severity of exercise. Am Rev Respir Dis. 1978;117(2):247-54.

84. Hahn AG, Nogrady SG, Tumilty DM, Lawrence SR, Morton AR. Histamine reactivity during the refractory period after exercise induced asthma. Thorax. 1984;39(12):919-23.

85. Lee TH, Nagakura T, Cromwell O, Brown MJ, Causon R, Kay AB. Neutrophil chemotactic activity and histamine in atopic and nonatopic subjects after exercise-induced asthma. Am Rev Respir Dis. 1984;129(3):409-12.

86. Barnes P, Brown M, Silverman M, Dollery C. Circulating catecholamine in exercise- and hyperventilation-induced asthma. Thorax. 1981;36(6):435-40.

87. Margolskee DJ, Bigby BG, Boushey HA. Indomethacin blocks airway tolerance to repetitive exercise but not to eucapnic hyperpnea in asthmatic subjects. Am Rev Respir Dis. 1988;137(4):842-6.

88. Reiff DB, Choudry NB, Pride NB, Ind PW. The effect of prolonged submaximal warm-up exercise on exercise-induced asthma. Am Rev Respir Dis. 1989;139(2):479-84.

89. Gilbert IA, Fouke JM, McFadden ER. The effect of repetitive exercise on airway temperatures. Am Rev Respir Dis. 1990;142(4):826-31.

90. Haby MM, Peat JK, Mellis CM, Anderson SD, Woolcock AJ. An exercise challenge for epidemiological studies of childhood asthma: validity and repeatability. Eur Respir J. 1995;8(5):729-36.

91. Silverman M, Anderson SD. Standardization of exercise tests in asthmatic children. Arch Dis Child. 1972;47(256):882-9.

92. Eggleston PA, Guerrant JL. A standardized method of evaluating exercise-induced asthma. J Allergy Clin Immunol. 1976;58(3):414-25.

93. Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, et al. Airway responsiveness: standardized challenge testing with pharmacological, physical sensitizing stimuli in adults. Eur Respir J. 1993;16:53-83.

94. Cropp GJ. The exercise bronchoprovocation test: standardization of procedures and evaluation of response. J Allergy Clin Immunol. 1979;64(6 pt 2):627-33.

95. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med.

2000;161(1):309-29.

96. Zach MS, Polgar G. Cold air challenge of airway hyperreactivity in children: dose-response interrelation with a reaction plateau. J Allergy Clin Immunol. 1997;80(1):9-17.

97. Anderson SD, Argyros GJ, Magnussen H, Holzer K. Provocation by eucapnic voluntary hyperpnoea to identify exercise-induced bronchoconstriction. Br J Sport Med. 2001;35(5):344-7.

98. Boulet LP, Legris C, Thibault L, Turcotte H. Comparative bronchial responses to hyperosmolar saline and methacholine in asthma. Thorax. 1987;42(12):953-8.

99. Avit A, Springer C, Bar Yishay E, Godfrey S. Adenosine, methacholine, and exercise challenge in children with asthma and chronic obstructive pulmonary disease. Thorax. 1995;50(5):511-6.

100. Holzer K, Anderson SD, Chan HK, Douglas J. Mannitol as a challenge test for exercise- and hyperventillation-induced asthma. Am J Respir Crit Care Med. 2003;167(4):534-7.

101. Parsons JB, Haustrand TS, Monstronarde JG, Kamisky DA, Randell KW, Hull JH, et al. An American Thoracic Society clinical practice guidelines: exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2013;187(9):1016-27.

102. Hargreave FE, Ryan G, Thomson NC, O'Byrne PM, Latimer K, Jupiter EF, et al. Bronchial responsiveness to histamine or methacholine in asthma in children. Comparison with histamine challenge. Eur Respir J. 1994;7:43-9.

103. Cockcroft DW, Davis BE, Todd DC, Smycniuk AJ. Methacholine challenge: comparison of two methods. Chest. 2005;127(3):839-44.

104. British Thoracic Society, British Paediatric Association, Research Unit of the Royal College of Physicians, King's Fund Centre, National Campaign, Royal College of General Practioners, et al. Guidelines for management of asthma in adults. I. Chronic persistent asthma. Thorax. 1993;48:(Suppl):S1-S24.

105. Cypcar D, Lemanske RF. Asthma and exercise. Clin Chest Med. 1994;15(2):351-68.

106. Katz RM. Prevention with or without the use of medications for exercise-induced asthma. Med Sci Sports Exerc. 1996;18(3):331-3.

107. Asthma and Allergy Foundation of America. America- Exercise-induced bronchoconstriction in Asthma.

108. Sinha T, David AK. Recognition and management of exercise-induced bronchospasm. Am Fam Physician. 2003;67(4):769-74, 675.

109. Higgs CM, Laszlo G. The duration of protection from exercise-induced asthma by inhaled salbutamol, and a comparison with inhaled reproterol. Br J Dis Chest. 1983;77(3):262-9.

110. Smith CH, Anderson SD, Seale JP. The duration of action of combination of fenoterol bromide and ipratropium bromide in protecting against provoked by hyperpnea. Chest. 1988;94(4):709-17.

111. Wooley M, Anderson SD, Quigley BM. Duration of protective effect of terbutaline and cromolyn sodium alone and in combination on exercise-induced asthma. Chest. 1990;97(1):39-45.

112. König P, Hordvik NL, Serby CW. Fenoterol in exercise-induced asthma. Effect of dose on efficacy and duration of action. Chest. 1984;85(4):462-4.

113. Tattersfield AE. Effect of beta-agonists and anticholinergic drugs on bronchial reactivity. Am Rev Respir Dis. 1987;136(4 Pt 2):S64-8.

114. Barnes PJ. New drugs for asthma. Clin Exp Allergy. 1996;26(7):738-45.

115. Anderson SD, Rodwell LT, Du Toit J, Young IH. Duration of protection by inhaled salmeterol in exercise-induced asthma. Chest. 1991;100(5):1254-60.

116. Carlsen KH, Rokund O, Skowronshi M, Ciufo R, Nova KR, McFadden ER. Effect of long-term salmeterol treatment on exercise-induced asthma in children. Eur Respir J. 1995;8:1852-55.

117. Green CP, Price JF. Prevention of exercise induced asthma by inhaled salmeterol xinafoate. Arch Dis Child. 1992;67(8):1014-17.

118. FDA drug safety communication: new safety requirement for long-acting asthma medications called long-acting beta-agonists. Washington (DC): US Food and Drug Association. 2010.

119. Pearlman D, Qaqundah P, Matz J, Yancey SW, Stempel DA, Ortega HG. Fluticasone/salmeterol and exercise-induced asthma in children with persistent asthma. Paediatr Pulmonol. 2009;44(5):429-35.

120. Chapman KR, Rennard SI, Dogra A. Long-term safety and efficacy of indecerol, a long-acting ß2-agonist in subjects with COOPD: a randomize placebo controlled study. Chest. 2011;140:68-75.

121. Hanania NA, Fedman G, Zachgo W, Shim JJ, Crim C, Sanford L, et al. The efficacy and safety of the novel long-acting ß2 agonist vilanterol in patients with COPD: a randomized placebo controlled trial. Chest. 2012;142(1):119-27.

122. Ferguson GT, Feldman GJ, Hofbauer P, Hamilton A, Allen L, Korducki L, et al. Efficacy and safety of olodaterol once daily delivered via Respimat® in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. Int J Chron Obstruct Pulmon Dis. 2014;9:629-45.

123. Anderson SD. Drugs and the control of exercise-induced asthma. Eur Respir J. 1993;6(8):1090-2.

124. Fuglsang G, Hertz B, Holm EB. No protection by oral terbutaline against exercise-induced asthma in children: a dose-response study. Eur Respir J. 1993;6(4):527-30.

125. Wright JM, Hancox RJ, Heebinson G, Cowan JO, Flanney EM, Taylor DR. Bronchodilator tolerance: the impact of increasing bronchoconstriction. Eur Respir J. 2003;21(5):810-5.

126. Haney S, Hancox RJ. Rapid onset of tolerance to beta-agonist bronchodilatation. Respir Med. 2005;99(5):566-71.

127. Haney S, Hancox RJ. Recovery from bronchoconstriction and bronchodilator tolerance. Clin Rev Allergy Immunol. 2006;31(2-3):181-96.

128. Weiler JM, Brannan JD, Randolph CC, Hallstrand TS, Parsons J, Silvers W, et al. Exercise-induced bronchoconstriction - update 2016. J Allergy Clin Immunol. 2016;138(5):1292-5.

129. Swystun VA, Bhagat R, Kalra S, Jennings B, Cockcroft DW. Comparison of 3 different doses of budesonide and placebo on the early asthmatic response to inhaled allergen. J Allergy Clin Immunol. 1998;102(3):363-7.

130. Simons FE, Gerster TV, Cheang MS. Tolerance to the bronchoprotective effects of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled corticosteroid treatment. Paediatrics. 1997;99(5):655-9.

131. Nelson HS. Beta-adrenergic bronchodilators. N Engl J Med. 1995;333(8):499-506.

132. Giembycz MA, Raeburn D. Putative substrates for cyclic nucleotide-dependent protein kinases and control of airway smooth muscle tone. J Autonomic Pharmacol. 1991;11(6):365-98.

133. Kume H, Hall IP. Washabau RJ. ß-adrenergic agents regulate K, Ca channels in airway smooth muscle by cAMP-dependent and -independent mechanisms. J Clin Invest. 1994;93:371-9.

134. Rhoden KJ, Meldrum LA, Barnes PJ. Inhibition of cholinergic neurotransmission in human airways by beta 2-adrenoceptors. J Appl Physiol (1985). 1988;65(2):700-5.

135. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. J Allergy Clin Immunol. 1996;97(1 Pt 2):169-76.

136. Dahl R, Lundaback B, Malo JR. A dose-ranging study of fluticasone

propionate in adult patients with moderate asthma. Chest. 1993;104(5):1352-58.

137. Waalkens HJ, van Essen-Zandvliet EEM, Gerritsen J, Duiverman EJ, Kerrebijn KF, Knol K. The effect of an inhaled corticosteroid (budesonide) on exercise-induced asthma in children. Eur Respir J. 1993;6(5):652-6.

138. World Anti-doping Agent. The World Anti-Doping Code: The 2010 Prohibited List: International Standard. 2010.

139. National Collegiate Athletic Association. NCAA burned drug list. 2010.

140. Krafczy MA, Asplund CA. Exercise-induced bronchoconstriction: Diagnosis and treatment. Am Fam Physician. 2011;84(4):427-37.

141. Silverman M, Andrea T. Time course of effect of disodium cromoglycate on exercise-induced asthma. Arch Dis Child. 1972;47(253):419-22.

142. Comis A, Valletta EA, Sette L, Andreoli A, Boner AL. Comparison of nedocromil sodium and sodium cromoglycate administered by pressurized aerosol, with and without a spacer device in exercise-induced asthma in children. Eur Respir J. 1993;6(4):523-6.

143. Spooner CH, Spooner GR, Rowe BH. Mast cell stabilizing agents to prevent exercise-induced bronchoconstriction. Cochrane Database Syst Rev. 2003;(4):CD002307.

144. Barnes PJ. Muscarinic receptor subtypes in the airways. Life Sci. 1993;53(5):521-8.

145. Godfrey S, Konig P. Suppression of exercise-induced asthma by salbutamol, theophylline, atropine, cromolyn, and placebo in a group of asthmatic children. Paediatrics. 1975;56:930-4.

146. O'Conor BJ, Towse LJ, Barnes PJ. Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. Am J Respir Crit Care Med. 1996;154(4):876-80.

147. Frew AJ, Holgate ST. Clinical pharmacology of asthma: implication for treatment. Drugs. 1993;46(5):847-62.

148. Barnes PJ. Cyclic nucleoside phosphodiesterase and airway function. Eur Respir J. 1995;8(3):457-62.

149. Cushley MJ, Tattersfield AE, Holgate ST. Adenosine-induced bronchoconstriction in asthma. Antagonism by inhaled theophylline. Am Rev Respir Dis. 1984;129(3):380-4.

150. Nicholson CD, Shahid M. Inhibitors of cyclic nucleotide phosphodiesterase isoenzymes: their potential utility in the therapy of asthma. Pulm Pharmacol. 1994;7(1):1-17.

151. Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. Physiol Rev. 1995;75(4):725-48.

152. Torphy TJ. Phosphodiesterase isoenzymes: molecular target for novel antiasthma agents. Am J Respir Crit Care Med. 1998;157(2):351-70.

153. Barnes PJ. Cyclic nucleotide phosphodiesterase and airway function. Eur Repir J. 1995;8(3):457-62.

154. Timmer W, Leclerc V, Birraux G, Neuhäuser M, Hatzelmann A, Bethke T, et al. The phosphodiasterase 4 roflumilast is efficacious in exercise-induced asthma and leads to suppression of stimulation of LPS-stimulated TNF-a *ex vivo*. J Clin Pharmacol. 2002;42(3):297-303.

155. Adelroth E, Inman MD, Summers E, Pace D, Modi M, O'Byrne PM. Prolonged protection against exercise-induced bronchoconstriction by leukotriene D4-receptor antagonist cinalukast. J Allergy Clin Immunol. 1997;99(2): 210-5.

156. Meltzer SS, Hasday JD, Cohn J, Bleecker ER. Inhibition of exercise-induced bronchospasm by zileuton: a 5-lipoxygenase inhibitor. Am J Respir Crit Care Med. 1996;153(3):931-5.

157. Edelman JM, Turpin JA, Bronsky EA, Grossman J, Kemp JP, Ghannam AF, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. Exercise Study Group. Ann Inter Med. 2000;132(2):97-104.

158. Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. N Engl J Med. 1998;339(3):147-52.

159. Raissy HH, Harkins M, Kelly F, Kelly HW. Pretreatment with albuterol versus montelukast for exercise-induced bronchospasm in children. Pharmacotherapy. 2008;28(3);287-94.

160. Philip G, Pearlman DS, Villarán C, Legrand C, Loeys T, Langdon RB, et al. Single-dose montelukast or salmeterol as protection against exercise-induced bronchoconstriction. Chest. 2007;132(3):875-83.

161. Pearlman DS, van Adelsberg J, Philip G, Tilles SS, Busse W, Hendeles I, et al. Onset and duration of protection against exercise-induced asthma by a single dose of montelukast. Ann Allergy Asthma Immunol. 2006;97(1):98-104.

162. Finnerty JP, Holgate ST. Evidence of the roles of histamine and prostaglandins as mediators of exercise-induced asthma: inhibitory effect of terfenadine and flurbiprofen alone and in combination. Eur Respir J. 1990;3(5):540-7.

163. Finnerty JP, Holgate ST. The contribution of histamine release and vagal reflexes, alone and in combination, to exercise-induced asthma. Eur Respir J. 1993;6(8):1132-37.

164. Manjara AI, Nel H, Majaraj B. Effect of desloratidine on patients with allergic rhinitis and exercise-induced bronchoconstriction: a placebo controlled study. J Asthma. 2009;46(2):156-9.

165. Pavord ID, Wisniewski A, Tattersfield AE. Inhaled frusemide and exercise induced asthma: evidence of a role for inhibitory prostanoids. Thorax. 1992;47(10):797-800.

166. Melo RE, Solé D, Naspitz K. Comparative efficacy of inhaled furosemide and disodium cromoglycate in the treatment of exercise-induced asthma. J Allergy Clin Immunol. 1997;99(2):204-9.

167. Novembre E, Frongia G, Lombardi E, Veneruso G, Vierucci A. The preventive effect of nedocromil or furosemide alone or in combination on exercise-induced asthma in children. J Allergy Clin Immunol. 1994;94(2):201-6.

168. Melilo E, Wooley KL, Manning PJ. Effect of inhaled PGE2 on exercise-induced bronchoconstriction in asthmatic subjects. Am J Respir Crit Care Med. 1994;149(5):1138-41.

169. Ahmed T, Gonzalez BJ, Danta I. Prevention of exercise-induced bronchoconstriction by inhaled low-molecular-weight heparin. Am J Respir Crit Care Med. 1999;160(2):576-81.

170. Corrigan CJ, Kay AB. T cells and eosinophils in the pathogenesis of asthma. Immunol Today. 1992;13(12):501-7.

171. Johansson MW. Activation states of blood eosinophils in asthma. Clin Exp Allergy. 2014;44(4):482-98.

172. Kucha E, Misiewicz K, Nitsch-such A, Kurpa D, Hon S, Szenborn L. Immunopathology of exercise-induced bronchoconstriction in athletes-a new modified hypothesis. Respir Physiol Neurobiol. 2013;187(1):82-7.

173. Cuoto M, Kurowski M, Moreira A, Bullens DMA, Carlsen KL, Delgado L, et al. Mechanisms of exercise-induced asthma in athletes: Current perspectives and future challenge. Allergy. 2018;73(1):8-16.

174. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011;365(12):1088-98.

175. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-66.

176. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al.

Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo controlled trial. Lancet. 2012;380:651-9.

177. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-207.

178. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371(13):1189-97.

179. Corren J, Weinstein S, Janka L, angrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil count. Chest Epub. 2016;150(4):799-810.

180. Bjermer L, Lemiere C, Maspero J, Weiss J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil level: a randomized phase 3 study. Chest. 2016;150(4):789-98.

181. Cabon Y, Molinari N, Morin G, Vachier I, Gamez S, Chanez P, et al. Comparison of anti-interleukin-5 therapies in patients with severe asthma: a global and indirect meta-analyses of randomized, placebo-controlled trials. Clin Exp Allergy. 2016;47(1):129-38.

182. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated eosinophils. Pulm Pharmacol Ther. 2017;43:39-45.

183. TEVA Pharmaceuticals Ltd. Reslizumab (CingaeroR (reslizumab). 2016.

184. Deeks ED, Brusselle G. Reslizumab in Eosinophilic Asthma: A Review. Drugs. 2017;77(7):777-784.

185. Beuther DA, Martin RJ. Efficacy of a heat exchanger mask in cold exercise-induced asthma. Chest. 2006;129(5):1188-93.

186. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. Chest. 2006;129(1):39-49.

187. Miller MG, Weiler JM, Baker R, Collins J, D'Alonzo G. National athletetic trainer's association position: management of asthma in athletes. J Athl Train. 2005;40(30:224-45.