Asthma in Athletes

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Abstract

Exercise-induced bronchoconstriction (EIB) is a very common disorder that may have considerable impact on the lives of those who suffer from its symptoms. Often, we contrast the significance of EIB on recreational versus competitive (or elite) athletes. Any athlete with EIB, from recreational to elite, Olympic, or competitive athletes, may have a comparable decrease in quality of life as a direct consequence of impaired overall exercise performance. EIB is an indicator of active and treatable airway pathophysiology consistent with asthma, identifying the presence of airway inflammation and sensitive airway smooth muscle. It also identifies airways that are treatable by pharmacotherapies that are successful in the treatment of asthma. It is important to identify objectively EIB in the athlete using standardized bronchial provocation tests as symptoms are not a useful diagnostic predictor of the presence or severity of EIB. It is important to treat EIB in a similar manner as treating asthma. Optimal treatment should not just decrease daily symptoms of asthma, but significantly attenuate or even abolish EIB. To achieve this, the health-care provider must understand the prevalence, pathophysiology, diagnostic modalities, and underlying mechanisms of EIB.

Keywords

Exercise-induced bronchoconstriction · Asthma · Athlete · Bronchial provocation testing

17.1 Introduction

The presence of active asthma in either a recreational or elite level athlete can manifest as exercise-induced bronchoconstriction (EIB). The presence of EIB can impact an individual's optimal exercise performance at best and at worst can put an individual at risk of a severe and possibly life-threatening attack of asthma. It is essential that the presence and severity of EIB be documented and treated optimally, with the goal to attenuate or abolish EIB.

EIB is the term used to describe the transient narrowing of the airways or bronchial hyperresponsiveness (BHR) that occurs either during exercise, although most commonly following, vigorous exercise. EIB can occur in persons with active asthma; however, it can also occur alone in the absence of daily asthma symptoms. Thus, EIB can commonly be seen in the elite or recreational athlete. Pharmacotherapy in the treatment of asthma is efficacious in the treatment of EIB, and there appear to be similarities in the airway pathophysiology. As EIB can be frequently documented in those with active asthma, it is thought to reflect insufficient control of the pathophysiology of underlying asthma. The prevalence of EIB can be difficult to determine in different populations and in different regions. However, in elite athletes the prevalence can be higher than observed in the general population. Further, the prevalence can also vary based on the intensity of the exercise or the environment (e.g., ambient conditions) where the exercise is performed.

Over the past two decades, significant advances in the understanding of the pathophysiology of EIB have been made. The increased hyperpnea caused by strenuous exercise is known to create a hyperosmolar airway surface via dehydration, resulting in compensatory water loss. This leads to a movement of water from the airway tissue into the lumen which is essential for heat loss. This leads to a hyperosmolar environment of the airway surface and likely to the submucosa, causing the release of bronchoconstricting mediators from inflammatory cells. Thus, the water content of the inspired air and the level of ventilation achieved and maintained during exercise are the major determinants of EIB. As a result of water loss, there are also alterations in airway temperature that can develop during exercise, but thermal factors are thought to have only a minor impact on the amount of bronchoconstriction that occurs. Thus, exercise per se is not needed to cause bronchoconstriction. Dry air hyperpnea in the absence of exercise, as well as the inhalation of an osmotic aerosol, can mimic the BHR that is observed with exercise.

Making the correct diagnosis of EIB is both challenging and essential. Overcoming these challenges is possible with a sound understanding of the advantages and limitations of diagnostic methods, combined with a good understanding of the pathophysiology of EIB. It is clear that symptoms alone are not sufficiently accurate to diagnose EIB. For example, dyspnea, a primary symptom of EIB, may exist due to poor exercise conditioning. Thus, objective testing of EIB has been recommended in order to document the presence and severity of BHR. These tests, also known as bronchial provocation tests (BPTs), include laboratory exercise testing using either treadmill running or a cycle ergometer, a surrogate hyperpnea test known as eucapnic voluntary hyperpnea (EVH), or challenging the airways in a dose-response manner with an osmotic aerosol (e.g., dry powder mannitol).

Therapeutic interventions for EIB have to consider both the acute protection and long-term treatment. Short-acting beta2-agonists (SABAs) are essential for reversal of bronchoconstriction and bronchoprotection. Additionally, anti-inflammatory medications including inhaled corticosteroids, leukotriene receptor antagonists (LTRAs), or combination therapy (with inhaled corticosteroids and long-acting beta2-agonists [LABAs]) are recommended for managing both BHR and airway inflammation. Unfortunately, the regular use of beta2-agonists can cause tolerance, limiting ability to provide optimal bronchoprotection, as well as complete and rapid rescue bronchodilation. A variety of alternative methods to prevent EIB have also been explored from exercise warm-up, use of face masks for minimizing airway water loss, and dietary modification. Alternative methods have shown different degrees of efficacy.

This review aims to be a guide for the successful identification and treatment of EIB. This chapter will focus on the athlete with asthma, but with relevance also regarding the athlete who does not have daily symptoms of asthma. It is both possible and essential for the correct diagnosis and treatment to be employed so that an athlete's performance is minimally impacted by the presence of BHR.

17.2 Prevalence of Exercise-Induced Bronchoconstriction

EIB is seen in either the presence or absence of chronic asthma in athletes or in individuals who are not otherwise competitive athletes. In most cases, exercise is the trigger for EIB so that many patients who otherwise have chronic asthma also have EIB when they exercise.

Often the criteria for the diagnosis of asthma also determine how many patients have EIB when tested. Thus, fall in FEV_1 with exercise, workload of exercise, and environmental conditions determine the percentage of patients diagnosed as having EIB. However, we must also take into consideration whether the subject being tested might have either a false-positive or false-negative diagnosis for EIB, which can be seen especially when symptoms rather than objective tests are used to make the diagnosis of EIB (Parsons et al. 2007, 2013; Rundell et al. 2001; Weiler et al. 2007). For these reasons, it has been recommended that indirect challenges such as exercise, EVH, or mannitol be performed to rule in or rule out EIB (Parsons et al. 2007, 2013; Rundell et al. 2001; Hallstrand et al. 2002; Weiler et al. 2016).

17.2.1 Prevalence in Nonathletes

When performing studies to estimate the prevalence of EIB in a nonathlete population, we must take into consideration the age, gender, and ethnicity of the subjects as well as their level of exercise performance (elite, competitive, or recreational). Season may also play a role in whether the challenge is positive (e.g., caused by exposure to ragweed or mountain cedar pollen) as well as environmental conditions (e.g., ambient temperature and humidity) (Parsons et al. 2013; Weiler et al. 2007; Mountjoy et al. 2015; Rundell et al. 2015).

In a study of 15,241 children that examined a 6-min free running test, participants recorded a fall in peak expiratory flow to diagnose EIB and a positive test was one in which the fall was at least 15%. It was observed that girls (8.5%) were

more likely than boys (6.4%) to have EIB and EIB was more prevalent in urban locations (8.9%) compared to rural settings (7.0%) (De Baets et al. 2005). Importantly, in all populations, symptoms alone poorly predicted a positive challenge. It is uncommon from other studies to observe gender differences in those having EIB, but, it has been shown that the frequency of EIB can decrease with increasing age (Bardagi et al. 1993).

It is unclear whether there are racial and ethnic differences in EIB prevalence. In one study using a standardized free running test and recording peak expiratory flow measurements, a higher prevalence of EIB was seen in African American (13%) compared with Caucasians (2%) (Kukafka et al. 1998). Using cycle ergometry, a study from Great Britain demonstrated that in 9-year-old children, those Asian children originating from the Indian subcontinent were 3.6 times more likely to have EIB than Caucasian inner-city children (Jones et al. 1996). A systematic review of 66 studies comprised of 55,696 participants assessing the prevalence of EIB in children confirmed findings of a high prevalence of EIB globally, with a 15% prevalence of EIB in children and adolescent athletes and 46% in children and adolescents with asthma (de Aguiar et al. 2018).

It has been reported that EIB in children may be the earliest symptom in the development of asthma (Sano et al. 1998; Cabral et al. 1999). In addition, the prevalence of EIB in school children may be 10–20% (Randolph 2013). EIB is significantly greater in children who are overweight and obese compared to non-overweight asthmatic children (Baek et al. 2011; van Veen et al. 2017). Further, BMI is a predictor of the severity of EIB in asthmatic boys (van Veen et al. 2017). Longitudinal studies have been performed that demonstrate increasing prevalence of asthma in children with EIB (Frank et al. 2008; Stern et al. 2008). Of interest are reports that parental observation of a history of exercise-induced wheezing and a presence of atopy are very strong predictors of asthma observed over 6 years of follow-up (Frank et al. 2008). In addition, a longitudinal birth cohort study reported that BHR to cold dry air in early childhood associated with an increased risk of chronic asthma was seen at 22 years of age (Stern et al. 2008).

An EVH challenge in adults may be a more potent test to identify EIB than a laboratory exercise challenge. A high prevalence of EIB in those who recreationally exercise (19% in 212 adults without a history of asthma) has been observed (Mannix et al. 2003), with another study finding a prevalence of 13% using EVH in 136 recreational athletes (Molphy et al. 2014). Further, a higher prevalence of EIB may be found in individuals with a family history of asthma (Godfrey and Konig 1975a). EIB is also more frequently documented in atopic individuals (Helenius et al. 1998; Sallaoui et al. 2009), including those who have allergic rhinitis (Brutsche et al. 1995). This was supported by studies showing EIB also occurs more frequently during and after respiratory viral infections and other respiratory diseases such as allergic rhinitis (Tilles 2003). Symptoms of EIB in some individuals vary depending on the time of year or season (Choi et al. 2012; Goldberg et al. 2005, 2012).

Microenvironments may play a role in the development of EIB so that exercise at an athletic field that has high air pollution or pollen counts may cause EIB (Mickleborough et al. 2007; Haverkamp et al. 2005). In one study, significant decreases in lung function in soccer players were related to months of daily measurements of air pollutants (Rundell et al. 2006). Emissions and particulate matter from vehicular traffic, as well as high levels of ambient ozone, can increase the airway responsiveness of EIB in asthmatics (McCreanor et al. 2007).

17.2.2 Prevalence in Athletes

EIB is commonly reported in athletes, especially in athletes who have asthma. The overall prevalence of EIB is reported to be from 30% to 60% (Cabral et al. 1999; Lazo-Velasquez et al. 2005; Benarab-Boucherit et al. 2011; Park et al. 2014). In patients with asthma, EIB in itself indicates lack of control of asthma and suggests the need to initiate or increase therapy or alternatively to encourage treatment adherence (Global Initiative

for Asthma 2007a). Depending on the sport and environment, the prevalence of asthma symptoms in elite athletes has been shown to vary from none to 61% (Rundell et al. 2000, 2001, 2004a; Parsons and Mastronarde 2005; Mannix et al. 1996; Rundell 2003; Wilber et al. 2000; Weiler et al. 1998; Weiler and Ryan 2000; Fitch and Morton 1971; Sue-Chu et al. 1999a; b; Pohjantahti et al. 2005; Randolph et al. 2006).

Both summer and winter elite endurance athletes have considerably more symptoms than athletes participating in non-endurance sports (Weiler et al. 1998; Weiler and Ryan 2000). However, it is difficult to determine if EIB is more common in winter compared to summer sporting activity. History forms required by the US Olympic Committee and completed by athletes participating in the 1996 Summer Olympic Games showed as many as 45% of summer athletes, depending on sport, answered questions compatible with having EIB (Weiler et al. 1998). Different sports showed varied prevalence, with endurance sports having higher prevalence rates and non-endurance sports having minimal levels. The same researchers found that as many as 61% of athletes participating in Nordic skiing events responded to questions that suggested they had EIB (Weiler and Ryan 2000).

17.2.2.1 Winter Athletes

High prevalence of EIB is reported in elite endurance athletes who perform exercise in cold environments such as competitive skaters and cross-country skiers (Pohjantahti et al. 2005; Anderson et al. 2003; Fitch et al. 2008). A similar high prevalence of EIB in Winter Olympic athletes has been reported based on objectively assessing EIB using an exercise BPT (Wilber et al. 2000). Ice skaters have a reported prevalence of EIB of 20–35%, which may be attributed to regular exposure of high emission pollution from ice cleaning equipment and cold dry air (Rundell 2003; Rundell et al. 2004a, 2007; Rundell and Caviston 2008). However, in cross-country skiers, the prevalence of EIB has been shown to be as high as 30–50% (Rundell et al. 2003). Others have found as many as 78% of elite cross-country skiers have symptoms of EIB and/or BHR (Larsson et al. 1993). The prevalence of both asthma and EIB may vary by gender in winter sport elite athletes. Frequency of EIB in females appears to exceed that of males. The prevalence of EIB by exercise challenge test was 26% in female and 18% in male athletes with a combined percentage of 23% in US Olympic winter sports (Wilber et al. 2000).

17.2.2.2 Summer Athletes

There also may be a high prevalence of EIB in summer athletes, dependent upon the type of sporting activity performed. In athletes who participated in the 1996 Summer Olympic Games, long-distance runners were found to have a prevalence of 17%, whereas speed runners had a prevalence of 8% (Helenius et al. 1997). For athletes who expend a similar amount of work, however, these differences may depend on how the test was performed rather than on a difference in the sports. None of the US Olympic divers and weightlifters had symptoms (by survey), while 45% of mountain bikers experienced symptoms. This difference in prevalence is consistent with the hypothesis that a higher prevalence of associated EIB during sport participation is found with endurance sports (Weiler et al. 1998). There is limited evidence to show differences in gender in athletes when using EVH as a surrogate challenge for EIB (Parsons et al. 2007; Couillard et al. 2014).

A high prevalence of EIB in summer athletes may also be associated with poor air quality (Helenius and Haahtela 2000). For swimmers, the chloramines used in swimming pools, which may be in high concentration in the air above the water, may trigger EIB. Swimmers with greater than 100 h of chlorinated pool exposure showed a higher prevalence of EIB (Bernard et al. 2009). Decreased incidence of EIB resulted from discontinuation of swimming (Helenius et al. 2002).

Seasonal variation of EIB is also described in Olympic summer athletes (Helenius et al. 1998). When using a reduced cutoff value for EIB of 6.5% fall in FEV_1 with running, 28% of runners had probable EIB. Of these athletes, 22% had EIB that happened only in the winter, and 7% reported EIB only during the pollen season (Helenius et al.

1998). It has also been shown that 35% of runners training in the cold reported a greater prevalence of EIB compared with a lower prevalence during the summer season (Ucok et al. 2004).

17.3 Mechanisms of Exercise-Induced Bronchoconstriction

The mechanisms of EIB have been elucidated over the last 55 years with significant controversy over the primary mechanisms of airway drying. Specifically, the controversy is between the "airway drying" or osmotic theory of EIB and the "airway cooling" or thermal theory of EIB (Godfrey and Fitch 2013). Currently it is thought that a period of high ventilation causes respiratory water loss along with cooling of the airways (Fig. 1). The result is a transient increase in the osmolarity of the airway surface liquid that occurs with a loss in volume of this liquid. These transient changes in osmolarity are rapidly resolved by the movement of water from the luminal side of the osmotically sensitive epithelium. The subsequent water loss from cells is thought to cause reduction in cell volume and the resulting regulatory volume increase, which includes increases in intracellular concentrations of calcium and inositol triphosphate, and is a requirement for the release of intracellular mediators (Eveloff and Warnock 1987). Cooling could provide a different stimulus which could induce reactive hyperemia of the bronchial vasculature (McFadden and Pichurko 1985). The response of the epithelium and other cells to the changes in airway surface liquid volume and the subsequent changes in osmolarity is the most likely trigger for the bronchoconstricting mediator release. Further, this mediator release is likely the primary stimulus for sustained bronchoconstriction following vigorous exercise (Hallstrand et al. 2012). Thus, it is important to consider that there may be some

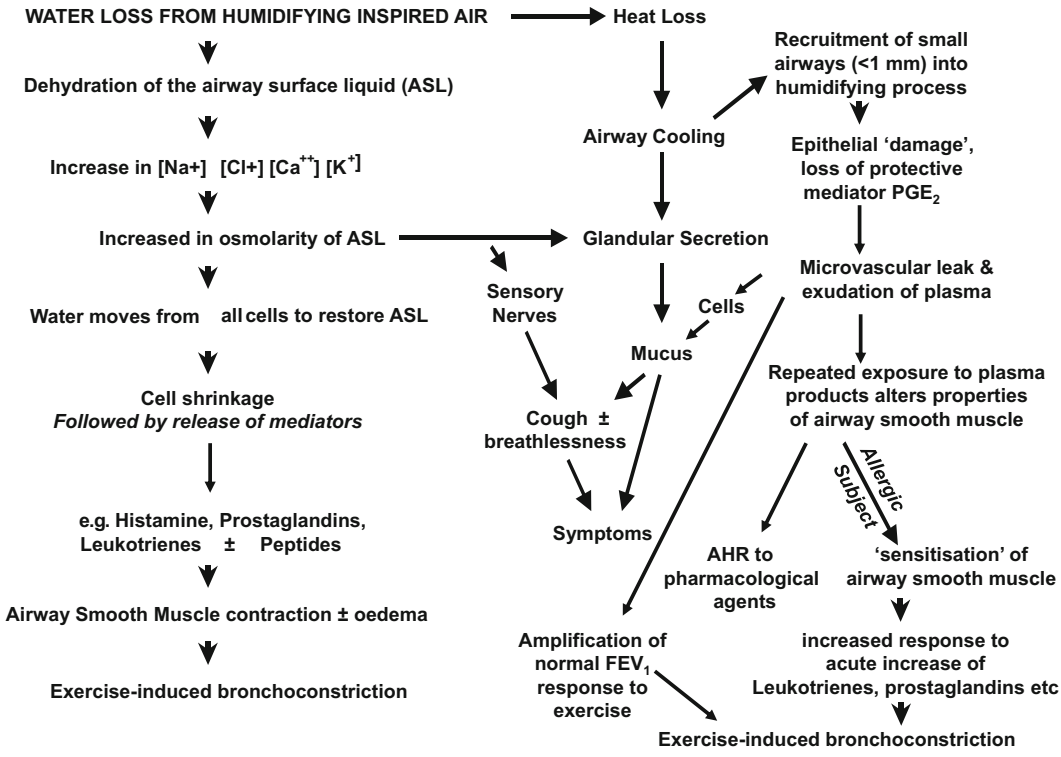


Fig. 1 Flow chart describing the acute events leading to EIB in the subject with classic asthma (left) and the events leading to the development of EIB in the athlete (right). (Reproduced with permission from (Anderson and Kippelen 2005))

contribution in certain extreme conditions of both the thermal and the osmotic theories of EIB. Under conditions of breathing cold dry air, vascular effects may result in airway edema and amplify the contractile effect of mediator release. Thus, the osmotic and vascular theories of EIB may operate together. It should be recognized that osmotic effects of water loss are more important than cooling, particularly as the temperature of the inspired air increases toward body temperature (Aitken and Marini 1985; Eschenbacher and Sheppard 1985; Tabka et al. 1988).

The thermal theory of EIB may be more relevant when subfreezing air is inspired during exercise. Then, airway cooling could induce vasoconstriction of the bronchial vasculature (McFadden and Pichurko 1985). When exercise ceases and ventilation falls, the airways rewarm, and reactive hyperemia with vascular engorgement and edema of the airway may occur (McFadden et al. 1986). The thermal theory of EIB is not sufficient to explain many of the events that occur in the airways following exercise challenge, in particular the sustained airway response and prolonged recovery of bronchoconstriction (Freed et al. 1995; Anderson and Daviskas 1992). Studies in canine models demonstrate that ligation of the bronchial circulation does not attenuate hyperpnea-induced bronchoconstriction, bringing into question the role of the bronchial vasculature (Freed et al. 1995). Studies in humans demonstrated that inspiring warm air following a BPT with cold air only had a modest effect on the degree of bronchoconstriction over 15 min after exercise (McFadden et al. 1986).

Because it was demonstrated that cooling of the airways was not a prerequisite for EIB, the osmotic theory of EIB was developed (Anderson 1992). Changes in airway surface osmolarity, with direct delivery of dry air (Freed and Davis 1999) or inhalation of osmotically active aerosols, were sufficient to cause BHR (Argyros et al. 1993; Freed et al. 1994; Brannan et al. 2003). Airway surface dehydration causes a temporary increase in ion content and osmolarity when water from the airway surface liquid is evaporated faster than it is returned by either condensation or via the epithelium or submucosa (Daviskas et al. 1991; Davis et al. 2003a). The exact mechanism by which the loss of water and resulting transient osmotic gradients lead to activation of inflammatory cells and mediator release is unclear. Mast cells (bound with cross-linked IgE) and eosinophils release mediators in response to changes in osmolarity (Gulliksson et al. 2006; Eggleston et al. 1987; Moloney et al. 2003). However, it is also now appreciated that changes in both airway surface volume and osmolarity also activate cellular signaling events in epithelial cells (Hallstrand et al. 2012). The release of regulatory epithelial proteins could lead to direct activation of other cells.

Voluntary hyperpnea of dry air induces bronchoconstriction similar to exercise in susceptible individuals; thus, exercise itself is not necessary to cause bronchoconstriction (Eliasson et al. 1992; Phillips et al. 1985). For athletes, EVH of dry air containing approximately 5% carbon dioxide can be used as a surrogate for exercise in the diagnosis of EIB in athletes (Parsons et al. 2007; Dickinson 2006; Stadelmann et al. 2011). Osmotic aerosols of hypertonic saline and mannitol can also cause bronchospasm in both asthmatic and athletic individuals and also can be used to aid in the EIB diagnosis. The relationship of the airway responses to these "surrogate" stimuli for EIB, and to an exercise provocation challenge test, is good in both asthmatic and athletic individuals with EIB (Brannan et al. 1998; Holzer et al. 2003; Munoz et al. 2008).

Many studies indicate that subjects with increased cellular inflammation are susceptible to EIB, supporting the concept that mediator release is important for EIB to occur. Inflammatory lipid mediators that have the capacity to cause bronchoconstriction via specific receptors on the airway smooth muscle are implicated in EIB. The induced sputum of adults and exhaled breath condensate (EBC) of children show the concentration of cysteinyl leukotrienes (CysLTs) C_4, D_4, and E_4 is increased with EIB (Hallstrand et al. 2005a; Carraro et al. 2005). CysLTs are elevated in EBC following exercise challenge (Bikov et al. 2010). Urinary LTE4 has been demonstrated to be released, and this release is sustained after exercise (Reiss et al. 1997;

Hallstrand et al. 2005b) (Fig. 2). Prostaglandins also play a significant role; specifically, prostaglandin D_2 (PGD_2) has been shown to be excreted in the urine after exercise (O'Sullivan et al. 1998a) and in association with the presence of leukotrienes in the airway response to dry air hyperpnea (Kippelen et al. 2010a) (Fig. 3). In contrast, prostaglandin E_2 (PGE_2) inhibits EIB when administered by inhalation (Melillo et al. 1994). The balance of these mediators may be important, as there is a possible reduction in the production of PGE_2 relative to CysLTs in patients with EIB (Hallstrand and Henderson 2010). Other mediators that may have a role in EIB but are not well understood are the nonenzymatic products of phospholipid oxidation, 8-isoprostanes, which are increased in EBC of individuals who have asthma with EIB (Barreto et al. 2009). Reduction in the formation of lipoxin A4, which is known to be a protective lipid mediator that may also play some role in the mechanism of EIB (Tahan et al. 2008). Individuals who have asthma who are susceptible to EIB, especially patients with atopy, often have elevated fraction of exhaled nitric oxide levels (Scollo et al. 2000; Malmberg et al. 2009).

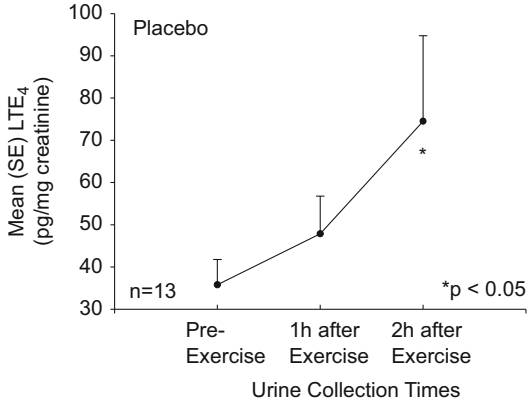


Fig. 2 The increase in the urinary excretion of metabolites of the leukotriene pathway, leukotriene E4 (pg per mg of creatinine), following a treadmill exercise challenge in 13 asthmatics; on a day placebo was administered in a study assessing the effectiveness of montelukast in the protection of EIB. (Reproduced with permission from (Reiss et al. 1997))

The formation of inflammatory eicosanoids such as CysLTs and PGD_2 is largely restricted to the myeloid cells; thus suggesting the intensity of airway inflammation in the airways may be an important factor in both EIB susceptibility and severity. There is an association with the degree of sputum eosinophilia and the severity of EIB (Duong et al. 2008). The severity of EIB is reduced after treatment with inhaled corticosteroid (ICS), which occurs with a reduction in percentage of eosinophils in sputum (Duong et al. 2008). Using genome-wide methods in patients with asthma has identified increased expression of mast cell genes in patients with EIB based on

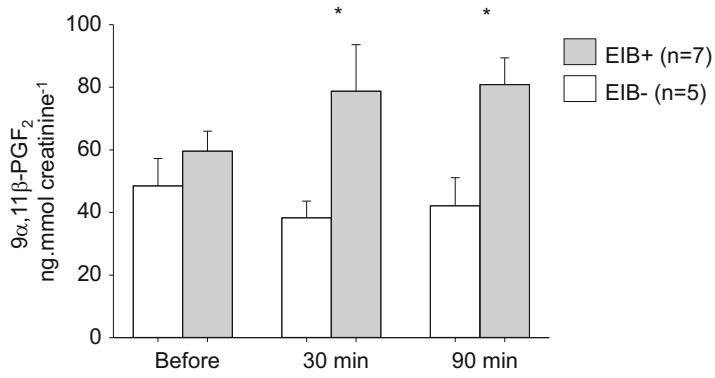


Fig. 3 The increase in the urinary excretion of a metabolite of prostaglandin D_2 and marker of mast cell activation, 9a,11b-PGF_2 (ng.mmol creatinine), following a cycle ergometer exercise challenge in seven asthmatics with EIB compared to five subjects who did not have EIB. (Reproduced with permission from (O'Sullivan et al. 1998b))

induced sputum and epithelial brushings (Lai et al. 2014). Increased expression of tryptase and carboxypeptidase A3, in the presence of relatively low chymase expression from epithelial brushings, indicates EIB is associated with Th2 high asthma (Woodruff et al. 2007; Dougherty et al. 2010). In patients who are susceptible to EIB, the density of intraepithelial mast cells per volume of the airway epithelium in endobronchial tissue of asthmatics is markedly elevated, suggesting a defining feature of EIB is mast cell infiltration of the airways (Lai et al. 2014). These more recent findings support a hypothesis that was developed in the early study of inhaled asthma drugs, where these drugs were thought to inhibit EIB acutely by inhibiting mast cells (Anderson et al. 1976). The rapid action of these drugs suggested to the investigators that the mast cell must have been located close to the airway surface.

Mast cells and eosinophils are well established as the major source of mediators in EIB (Reiss et al. 1997; Hallstrand et al. 2005b; O'Sullivan et al. 1998a). Mast cells generate de novo prostaglandin D_2 and leukotrienes and release stored histamine. Eosinophils are also a major source of leukotrienes and if present in high number may contribute to the increased severity of EIB (Duong et al. 2008). The immediate effect of these mediators is to constrict airway smooth muscle; however, they play other roles in activating sensory nerves, mucus secretion, and increasing microvascular permeability leading to airway edema (Hallstrand and Henderson 2010). It is not clear that they play a role in worsening airway inflammation acutely as there are no known late phase responses to exercise (Gauvreau et al. 2000). The first observations suggested small increases in arterial histamine in response to exercise (Hartley et al. 1981; Anderson et al. 1981). More recent studies using modern sampling methodology that allow more direct sampling of the airway using induced sputum found mast cell degranulation occurs with the release of histamine and tryptase during EIB (Hallstrand et al. 2005b; Haverkamp et al. 2007; Anderson and Brannan 2002).

Pharmacological treatments have played an important role in elucidating the mechanism of EIB and the role of bronchoconstricting mediators. Histamine antagonists have incomplete protection against EIB, suggesting histamine is a relatively weak mediator (Hallstrand et al. 2005b; Patel 1984; Baki and Orhan 2002; Dahlén et al. 2002). The development of leukotriene receptor antagonists revealed that leukotrienes play an important role in EIB, particularly in sustaining the airway response after exercise (Reiss et al. 1997; Leff et al. 1998). Thus, the response of a $CysLT_1$ receptor antagonist in EIB is to reduce both the maximum fall in FEV_1 and the time of recovery to baseline lung function after EIB (Leff et al. 1998; Pearlman et al. 2006). The 5-lipoxygenase inhibitor, zileuton, when administered four times daily over 2 days, also reduced the fall in FEV_1 after exercise challenge by approximately 50% (Meltzer et al. 1996). A role for CysLTs in the pathogenesis of EIB is clearly demonstrated by these results, but they also indicate the protection from EIB is incomplete. This again suggests that other mediators may play a role (e.g., PGD2) (Brannan et al. 2006; Simpson et al. 2016). The cromolyn drugs are thought to protect primarily via stabilizing mast cells and preventing mediator release (Kippelen et al. 2010a; Brannan et al. 2006). Following EVH challenge, the metabolite of PGD2, 9α, 11beta-PGF2 is increased in the urine, and the release of PGD2 can be inhibited by either pretreatment with a high dose of inhaled steroid or with a cromone (Kippelen et al. 2010a, b).

Sensory nerves also are thought to play a role, but there is less direct evidence for effects on EIB. Sensory nerve endings within the epithelium may be activated directly by a variety of mechanisms such as changes in osmolarity, the mechanical effects of bronchospasm, or in response to other mediators in the airways that could cause the release of neurokinins. Sensory nerves could send signals from the airways to the central nervous system, but they can also act locally via retrograde axonal transmission that could lead to bronchoconstriction and the production of mucus. Sensory nerves can either be directly activated or have the activation threshold altered by eicosanoids such as CysLTs (Taylor-Clark et al. 2008). Animal models of hyperpnea-induced

bronchoconstriction (HIB) have shown leukotriene antagonists inhibit both the release of neurokinins and HIB. Neurokinin receptor antagonists inhibit the development of HIB without changing neurokinin levels consistent with leukotriene-mediated bronchoconstriction that occurs via sensory nerve activation (Freed et al. 2003; Lai and Lee 1999). Human studies of neurokinin 1 antagonists have given varied results in the presence of BPTs using exercise and hypertonic saline (Fahy et al. 1995; Ichinose et al. 1996), which may be due to the predominance of the neurokinin 2 receptor (Naline et al. 1989). Release of the major gel-forming mucin MUC5AC following exercise challenge is associated with the levels of CysLTs in the airways and the levels of CysLTs and neurokinin A are correlated after exercise (Hallstrand et al. 2007).

Following exercise there is an interval of refractoriness lasting approximately 1–3 h during which additional exercise produces less bronchoconstriction in approximately half of patients who have EIB (Mickleborough et al. 2007; Haverkamp et al. 2005; Edmunds et al. 1978). This protection has been shown to be additive to the protective effect of pretreatment with a SABA (Mickleborough et al. 2007). Thus, warm-up exercise prior to competition may be useful to further attenuate EIB (Elkins and Brannan 2013). The mechanism of the refractory period is not well understood, and there could be multiple pathways and explanations. An early explanation for the refractory period was that it induces the generation of protective prostaglandins (e.g., release of PGE_2). It was found that when nonsteroidal anti-inflammatory drugs were administered that inhibit the cyclooxygenase pathway, the refractoriness to both exercise and leukotriene D_4 challenge was reduced (Manning et al. 1993; Wilson et al. 1994). There is now evidence for PGE2 being released in the urine during the refractory period to EVH challenge that supports these earlier observations (Bood et al. 2015). However, two separate studies using mannitol or EVH found that the protective effect to a repeat challenge could be explained by possible tolerance at the site of the airway smooth muscle (Bood et al. 2015; Larsson et al. 2011).

17.3.1 The Regular Effect of Vigorous Exercise: The Potential Role of Airway Damage

Athletes engaged in swimming, mountain biking, rowing, biathlon, cross-country skiing, and skating events (i.e., either winter or summer sports with high ventilation rates) may develop respiratory symptoms compatible with EIB alone. These athletes also may or may not demonstrate a positive exercise, EVH, or mannitol challenge test result indicative of EIB or asthma (Sue-Chu et al. 2010). Changes in the contractile properties of the bronchial smooth muscle as a result of exposure to plasma-derived products from exudation may result from the repetitive epithelial injury repair cycle that arises in response to breathing high volumes of unconditioned air over long periods (Sue-Chu et al. 1999a; Anderson and Kippelen 2008; Karjalainen et al. 2000) (Fig. 1). In contrast to EIB, which results from airway smooth muscle constriction from the osmotic release of bronchoconstricting mediators from resident inflammatory cells (e.g., mast cells, eosinophils), this may be representative of an "airway injury" resulting in a form of "overuse syndrome." With winter athletes, it is common to see a low prevalence of BHR to indirect tests but high prevalence of BHR to direct challenge tests such as methacholine, which in this situation suggests the presence of airway damage (Sue-Chu et al. 2002, 2010; Stensrud et al. 2007). Treatment recommendations for suspected airway injury in an athlete may include the limitation of activity, rather than the introduction of the pharmacological agents used in the treatment of asthma and EIB (Bougault et al. 2010; Hull et al. 2009).

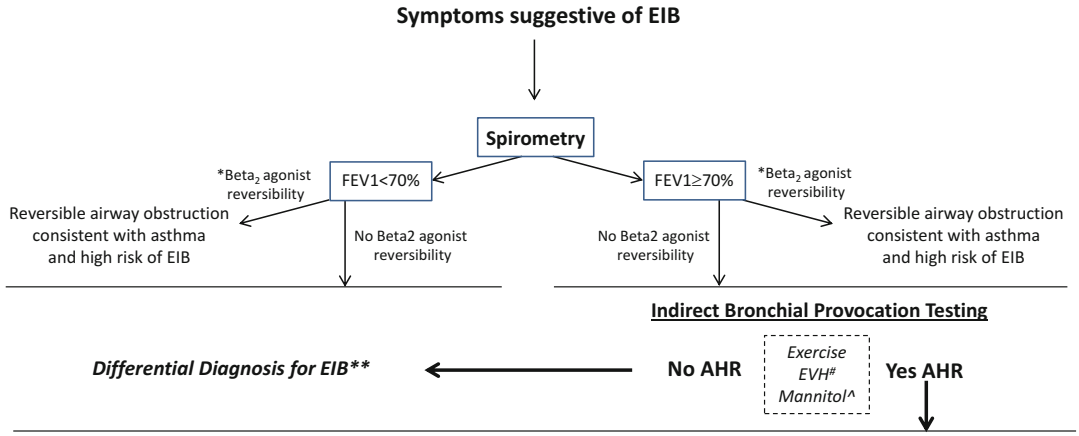
For summer athletes with allergic sensitization, the conditioning of large volumes of air may lead to airway inflammatory cell recruitment as well the consequences of plasma exudation leading to passive sensitization of the bronchial smooth muscle, possibly due to higher levels of seasonal airborne allergen (Anderson and Kippelen 2008). In contrast to the winter athlete, summer athletes generally demonstrate lower rates of BHR to direct tests (Holzer et al. 2002; Pedersen et al. 2008) and higher rates of BHR to indirect tests,

which has led to suggestions that elite level exercise in these environments may promote EIB in susceptible individuals (Kippelen and Anderson 2013).

17.4 Diagnosis of Exercised-Induced Bronchoconstriction

Wheeze, chest tightness, shortness of breath (dyspnea), and cough are the primary symptoms of EIB. Symptoms can also include chest pain in children as well as excessive mucous production. Some patients will report feeling unfit despite being in good physical condition (Parsons et al. 2007; Rundell et al. 2001; Weiler et al. 2007; Carlsen et al. 2000; Weinberger and Abu-Hasan 2009). A diagnosis of EIB based on symptoms is not reliable to predict a positive exercise challenge in either adults or children, because these symptoms also occur with other conditions (Rundell et al. 2001; De Baets et al. 2005; Anderson et al. 2010; van Leeuwen et al. 2013; Simpson et al. 2015). Given the lack of diagnostic sensitivity and specificity, symptom-based diagnosis alone should be avoided, and it is preferable that it be accompanied by data from an objective exercise or surrogate BPT such as EVH or mannitol (Parsons et al. 2007; Rundell et al. 2001; Weiler et al. 2007; Carlsen et al. 2000; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009) (Figs. 4 and 5).

There are two types of BPTs used to identify airway hyperresponsiveness based on mechanism of action: direct and indirect challenges. Direct challenges involve the exogenous administration of a single pharmacological agent as a provoking substance (such as methacholine), which acts directly via receptors on airway smooth muscle to cause contraction. For indirect challenges, the provoking agent causes the endogenous release of bronchoconstricting mediators that target specific receptors to cause the airway smooth muscle to contract. Indirect challenges include exercise or a surrogate, such as EVH, or an inhaled osmotic agent such as mannitol or hypertonic saline. It is now clear that a variety of mediators are released with indirect stimuli, such as leukotrienes, prostaglandins, and histamine (Anderson et al. 2018). BHR that is caused by the presence of airway inflammation is reflected more specifically in indirect challenges; thus indirect challenges are preferred as a way to confirm underlying asthma and potentially the need for regular inhaled corticosteroids (Parsons et al. 2007; Rundell et al. 2001; Weiler et al. 2007; Carlsen et al. 2000; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009). Indirect challenges additionally are recommended for monitoring asthma therapy because BHR is caused by airway inflammation (Parsons et al. 2007; Rundell et al. 2001; Carlsen et al. 2000; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009) which is diminished by ICS therapy (Weiler et al. 2007; Cockcroft and Davis 2009; Koh et al. 2007; Subbarao et al. 2006; Lipworth et al. 2012). In contrast, direct challenges are used as a screening test for chronic asthma, especially to rule out asthma. Direct challenges reflect the effect of only a single agonist or mediator and can have a low sensitivity and specificity to detect EIB, thus limiting their use (Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000; Cockcroft and Davis 2009; Anderson et al. 2009; Holley et al. 2012). An individual who has a positive direct BPT, current active symptoms of asthma, demonstrated airway reversibility with spirometry, and/or has other markers of airway inflammation (e.g., raised exhaled nitric oxide, sputum eosinophils) will likely have EIB. While there is an association with FeNO and percent fall in FEV_1 to exercise in atopic patients (Rouhos et al. 2005), FeNO should be used with caution to predict EIB when considering FeNO as a substitute for an indirect challenge. FeNO is a weak predictor of a positive EVH challenge in athletes (Voutilainen et al. 2013). Further, some ICS-naïve asthmatics with BHR to mannitol can have normal FeNO values (Porsbjerg et al. 2008). It is for this reason that guidelines recommend the use of physiological tests to assess BHR, in particular indirect tests to document both the presence and severity of EIB (Weiler et al. 2016).



Grade Severity of AHR

Laboratory Exercise		Eucapnic Voluntary Hyperpnea		Mannitol	
Fall in FEV1	*Classification*	*Fall in FEV1*	*Classification*	*PD15*	*Classification*
>50%	severe	>50%	severe	< 35mg	severe
25-50%	moderate	25-50%	moderate	35-155mg	moderate
>10-25%	mild	>10-25%	mild	155-635mg	mild
< 10%	no EIB	< 10%	no AHR If Ve >60%MVV	No PD_{15}	No AHR
				PD10 only may suggest mild EIB	

Legend:

FEV1 – Forced expiratory volume in 1 second, AHR – Airway hyperresponsiveness, EVH – Eucapnic Voluntary Hyperpnea , PD15 – the provoking dose of mannitol to cause a 15% fall in FEV1, PD10 – the provoking dose of mannitol to cause a 10% fall in FEV1. * Demonstrating reversibility in FEV1 of 12% and 200mL or greater., # FEV1≥75% for EVH challenge, ^Subject to availability in the USA, **Very mild AHR may cause variable responses to all tests and if EIB is still strongly suspect a repeat test may be warranted.

Fig. 4 An algorithm for the decision to perform an indirect bronchial provocation test in persons with symptoms suggestive of EIB, including the test options and test outcomes, which include the cutoff values for a positive test and the classification of the airway response to grade severity of AHR. (Adapted from (Weiler et al. 2016) and taken from (Brannan and Porsbjerg 2018)) (*FEV1* Forced expiratory volume in 1 s, *AHR* Airway hyperresponsiveness, *EVH* Eucapnic Voluntary Hyperpnea, *PD15* the provoking dose of mannitol to cause a 15% fall in FEV1, *PD10* the provoking dose of mannitol to cause a 10% fall in FEV1. * Demonstrating reversibility in FEV1 of 12% and 200 mL or greater, # FEV1 $\geq$ 75% for EVH challenge, ^Subject to availability in the USA, **Very mild AHR may cause variable responses to all tests and if EIB is still strongly suspect a repeat test may be warranted)

17.4.1 Exercise Challenge Testing

Exercise challenge testing should be conducted only by trained personnel and using standardized protocols, which also often require the presence of trained medical personnel. Exercise BPTs in a laboratory should be performed as described in the consensus statement published by the American Thoracic Society (ATS) and American Academy of Allergy, Asthma, and Immunology (AAAAI) (Parsons et al. 2013; Weiler et al. 2016; Crapo et al. 2000). For all BPTs, in order to avoid influencing the airway response, treatments that are effective at attenuating or inhibiting BHR should be withheld for an appropriate time prior to testing to ensure sufficient washout of the drug. Withholding times have been reviewed in recent guidelines (Weiler et al. 2016).

It is essential that adequate exercise laboratory challenges control minute ventilation and water content of inhaled air (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000). If this is not achieved, it will lead to a decreased sensitivity of the testing procedure. Exercise ramp-up should be rapid, within 2–3 min, to reach quickly a heart rate of 85% of

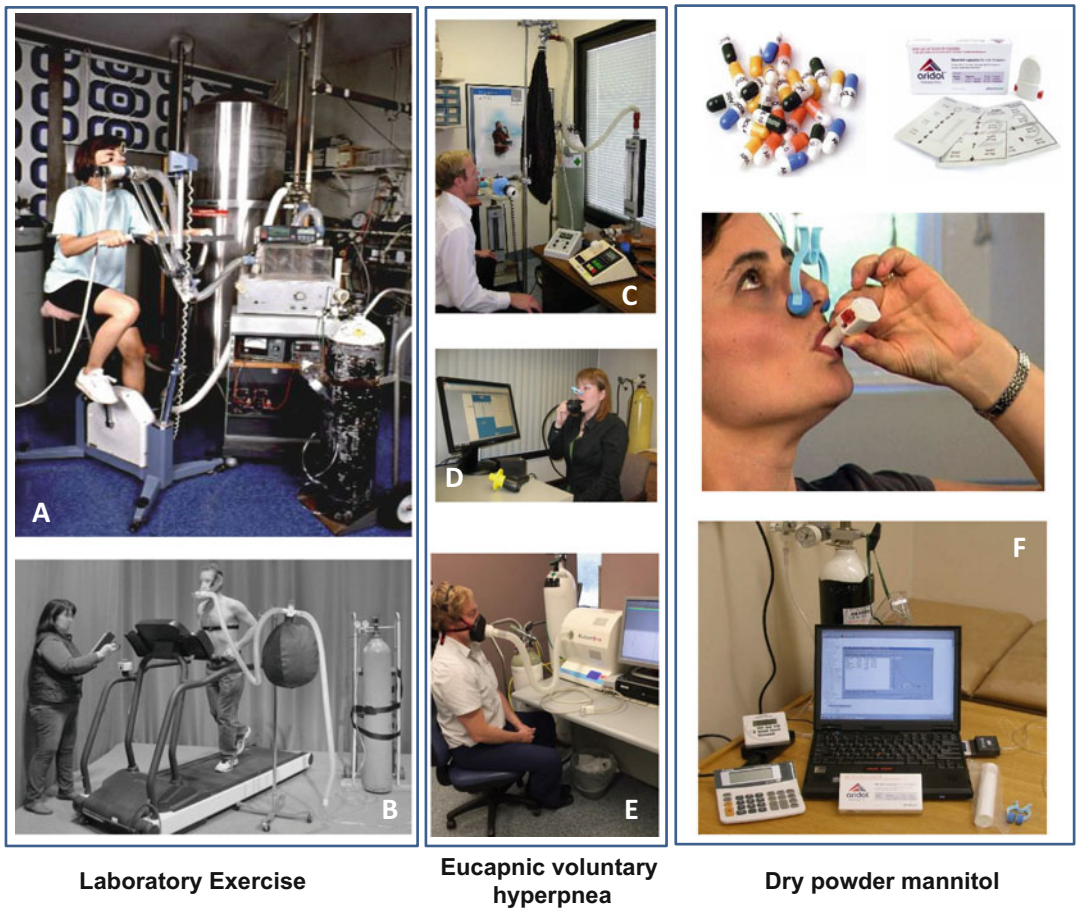


Fig. 5 An example of equipment required to perform laboratory exercise, eucapnic voluntary hyperpnea or inhaled mannitol challenge testing. Exercise challenge testing; (**a**) cycling exercise using a cycle ergometer; (**b**) running exercise using a treadmill, eucapnic voluntary hyperpnea; (**c**) noncommercial system using sourced equipment; (**d**) commercial device known as the hyperventilometer; (**e**) commercial device known as the EucapSys system; (**f**) mannitol challenge test kit and supporting equipment. (Adapted from (Brannan and Porsbjerg 2018))

maximum for adults and up to 95% for children. Exercise should continue at this rate for an additional 6 min, at 20–25 °C, while breathing dry (medical grade) air to provide a surrogate for at least 40% of maximum voluntary ventilation (MVV) (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000). However, the exercise ventilation ideally should be above 60% of predicted maximum (i.e., greater than 21 times FEV_1) (Parsons et al. 2013; Rundell and Slee 2008; Crapo et al. 2000). Medical air can be supplied to a balloon reservoir bag (e.g., Douglas bag) fitted with a two-way non-rebreathing valve before being attached to a mouthpiece or face mask. Alternatively it can be supplied directly from a compressed air tank with a demand valve that delivers air at high flow rates (Anderson et al. 2001; Weiler et al. 2005). The level of ventilation reached and sustained is key to providing a maximal stimulus, and thus the measurement of ventilation should be encouraged (Anderson and Kippelen 2013). Minute ventilation of expired air may be measured in real time by using a high flow spirometer or metabolic cart. Maximal heart rate (HR) may be used alternatively and is estimated using the formula

220 – age (in years). A more accurate equation to predict HRmax (208 – 0.7 × age) was recently recommended (Weiler et al. 2016). The exercise intensity may be required to be above a 90% HRmax for very well-conditioned individuals. Adolescent children may need to reach a higher target HRmax of 95% as one study in 9–17-year-olds demonstrated the fall in FEV_1 was 25.1% at 95% HRmax but 8.8% when only 85% HRmax was reached (Carlsen et al. 2000).

Spirometry should be obtained at baseline, before exercise challenge, and at predetermined times after exercise, usually at 5, 10, 15, 30, and occasionally 45–60 min after exercise. Spirometry should be performed seated. For reasons of safety, a measurement at 1 and/or 3 min post exercise may be warranted in persons who may be suspected of having large falls in FEV_1. To avoid causing the patient to become tired by the spirometry efforts and thus limiting the quality of subsequent measurements, FEV_1 measures are often performed by the patient without full forced vital capacity (FVC) maneuvers at the post-exercise time points. FEV_1 should be recorded beginning as soon as 3 min after completion of the exercise challenge to overcome the problem of posttest respiratory fatigue. To obtain a pre-exercise value, a full FVC maneuver is performed at baseline (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000). EIB may be diagnosed with a 10% or greater fall in FEV_1 from the pre-exercise value at any two consecutive time points within 30 min of ceasing exercise (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000; Anderson and Kippelen 2013). A fall at only one time point may be considered diagnostic of EIB if a greater fall in FEV_1 is required (such as an FEV_1 fall of 20% as in some pharmaceutical studies) (Anderson et al. 2001).

To determine whether the fall is sustained and not the product of a single measurement that may represent an artifact due to inadequate spirometry effort at one or more time points, the profile of the fall in FEV_1 following an exercise or EVH challenge should be carefully examined. In those with milder BHR, it is important to note that there may be variability in the airway response to exercise when more than one test is performed. Thus, in some cases where EIB is strongly suspected or when the patient is treated optimally and evidence of the abolition of EIB is required, repeat testing may need to be considered (Weiler et al. 2016; Anderson et al. 2010; Anderson and Kippelen 2013; Price et al. 2015).

All individuals who have EIB cannot be identified with any single test (Weiler et al. 2007). Individuals who are subsequently found to have other conditions may show falls in FEV_1 that are consistent with EIB (Weiler et al. 2007). For example, an upper airway dysfunction may be suggested by a flat or "truncated" inspiratory flow volume loop on the flow volume curve rather than EIB (Weiler et al. 2007). EIB may occur independently or coexist with exercise-induced laryngeal dysfunction. It may be important to document changes in FVC in some cases to identify if a fall in FEV_1 is due to upper airway dysfunction limiting the patient's inhalation to total lung capacity (TLC). Protocols to identify potential exercise-induced laryngeal dysfunction may need to be followed and this condition to be investigated separately (Weiler et al. 2016).

Exercise challenge by treadmill is easily standardized for office practice, though more commonly performed in a hospital laboratory. Alternative exercise challenges using cycle ergometry or rowing machine may be performed. Compared to the treadmill challenge, cycle exercise may provide a suboptimal exercise stimulus (Anderson and Kippelen 2013). Further, field and free running challenge tests are an option and have been used to screen larger numbers of patients. These protocols are more difficult to standardize and present difficulties in both documenting and guaranteeing an optimal exercise intensity and airway dehydration stimulus (Parsons et al. 2013; Weiler et al. 2007; van Leeuwen et al. 2013; Rundell and Slee 2008; Crapo et al. 2000).

In spite of sport governing bodies requiring specific cutoff values to diagnose EIB, there is no single absolute cutoff for a fall in FEV_1 or change in some other spirometry measure that clearly and unequivocally distinguishes between the presence of EIB and the absence of EIB (Weiler et al. 2007). The ATS criteria suggest the

post-exercise fall in FEV_1 required to make the diagnosis must be at least 10%, whereas other groups have suggested a fall of 13–15% is necessary to make the diagnosis (Parsons et al. 2013; Rundell and Slee 2008; Crapo et al. 2000). Other recommendations also include a fall in FEV_1 of 15% after a "field" challenge and a fall of 6–10% in the laboratory (Parsons et al. 2013; Weiler et al. 2007; Rundell and Slee 2008; Crapo et al. 2000).

17.4.2 Surrogate Tests for EIB

Organizations that regulate drug use by elite athletes or professional bodies needing to assess the presence of EIB by occupation are increasingly recommending the use of surrogate challenges for exercise such as EVH (ungraded challenge) or an inhaled hyperosmolar agent such as mannitol (graded challenge). While EVH is a challenge test that should be used for the investigation of EIB alone, inhaled mannitol may be useful in identifying both EIB and the presence of active asthma (Anderson 2010, 2016) (Fig. 6). Inhaled mannitol, commercially available as a disposable kit (Aridol™ or Osmohale™) (Aridol™ 2017), has undergone extensive phase 3 testing (Anderson et al. 2009; Brannan et al. 2005) establishing safety and has been recognized by regulatory authorities in Australia, the United States, European Union, Korea, and other regions. At the time of writing, Aridol™ will be reintroduced into the wider US market in late 2018.

17.4.3 Eucapnic Voluntary Hyperpnea

The EVH challenge was developed based on the understanding that the ventilation reached and sustained and the water content of the air inspired are the most important determinants of EIB (Anderson and Daviskas 2000). The EVH test was developed initially to evaluate military recruits for EIB (Argyros et al. 1996). The European Respiratory Society/European Academy of Allergy and Clinical Immunology Task Force (Carlsen et al. 2008a) recommend EVH to identify EIB in athletes, and EVH is included in the World Anti-Doping Agency assessment of asthma.

All safety precautions should be observed during an EVH test and should only be performed by highly trained specialists. For those with

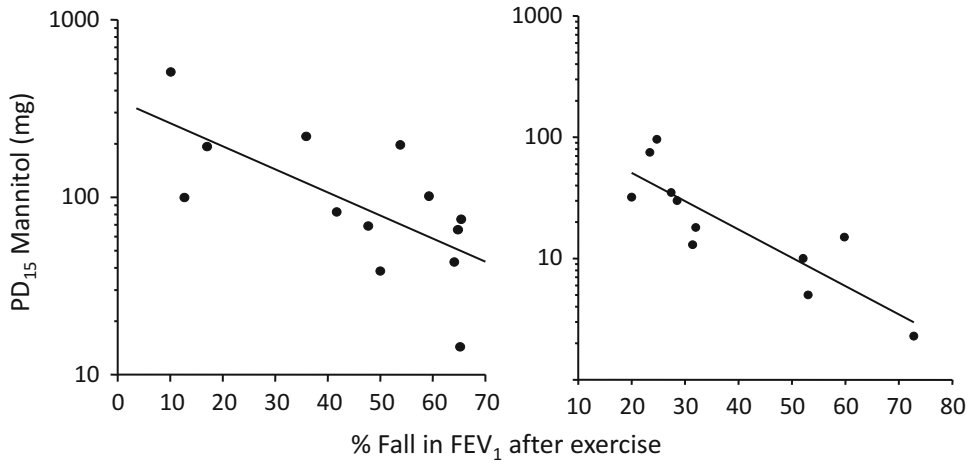


Fig. 6 In steroid-naïve asthmatics, the relationship demonstrating satisfactory agreement between the percent fall in FEV_1 after a cycle exercise challenge and the airway sensitivity to inhaled mannitol (PD_{15}) in two separate studies (Brannan et al., $n = 13$, rp 0.68, $p < 0.01$ and Munoz et al., $n = 11$ rp $= 0.86$, $p < 0.001$). These studies highlighted further the safety of mannitol challenge testing, only requiring a 15% fall in FEV_1 compared to significant falls in FEV_1 to exercise in some of these asthmatic subjects. (Reproduced with permission from (Brannan et al. 1998))

established asthma who are experiencing frequent symptoms and require beta2-agonists to alleviate those symptoms, the EVH test should be performed with caution knowing that the stimulus may cause significant bronchospasm in these susceptible patients. The EVH test should not be performed on patients in whom the FEV_1 is less than 75% of predicted (Parsons et al. 2013; Weiler et al. 2007, 2016; Rundell and Slee 2008; Crapo et al. 2000).

When performing the EVH test, the patient voluntarily hyperventilates a source of dry air containing approximately 5% carbon dioxide to maintain eucapnia, with the remainder of the gas mixture containing 21% oxygen and the balance nitrogen (Phillips et al. 1985). The characteristics of the airway response to EVH are very similar to exercise. The patient's maximum level of ventilation can be reached more rapidly with voluntary hyperventilation, reducing the required time for the EVH test in comparison to the exercise challenge.

An EVH challenge requires less space and equipment than an exercise challenge. Noncommercial or homemade systems similar to those that were first developed for EVH are still in use (Anderson and Kippelen 2013). The required apparatus can be easily sourced, and the initial setup is relatively inexpensive compared with exercise challenge equipment. Real-time measurement of ventilation is recommended, and a pre-prepared gas mixture is required which adds to the cost of the test. This system requires a large meteorological balloon as a gas reservoir, and the balloon is filled with at least 90 L of the dry air mixture containing 5% CO_2. The patient inhales the air via a two-way valve and is encouraged to hyperventilate sufficiently to keep the balloon at a constant volume, while the gas from the cylinder refills the balloon via a rotameter at the target ventilation. This system provides constant feedback to patient on their ventilation rate, while the investigator can encourage "deeper" or "faster" breathing if required. This mixture keeps end-tidal CO_2 levels within the normal or eucapnic range between 40 and 105 L/min in patients with FEV_1 values greater than 1.5 L (Phillips et al. 1985). If a subject, such as an elite athlete, has a level of ventilation value beyond this range, then a mixing device can be used to adjust and monitor the CO_2 concentration to maintain eucapnia. It is important that eucapnia (38–42 mmHg) is maintained during an EVH challenge as hypocapnia has long been known as a stimulus for bronchoconstriction (O'Cain et al. 1979). Commercial systems now exist that also require gas mixtures that use a demand valve directly attached to the source of gas, with incentive devices on computer screens to help the subject achieve the target ventilation. Another commercial system permits the breath-by-breath delivery of dry air with the addition of CO_2 (SMTEC 2014). These systems may be cheaper to run in the long term as separate sources of dry air and CO_2 are cheaper than a pre-prepared gas mixture.

While there are a number of different protocols for EVH, the most accepted standardized protocol uses a pre-prepared gas mixture inhaled at room temperature for 6 min (Parsons et al. 2013; Weiler et al. 2016). The target ventilation is 30 times the baseline FEV_1, and it has been demonstrated that the majority of patients are able to achieve this target. The minimum level for a valid test may be set as low as 17.5 times the FEV_1 for 6 min to be consistent with exercise ventilation. If the minimum ventilation is not reached, however, the test may be invalid and need repeating. Cooling the air can reduce the time of the challenge, but it is an expensive addition that is unnecessary for most assessments. At the end of the period of ventilation, FEV_1 is measured in duplicate immediately post-challenge and at 3, 5, 10, 15, and 20 min.

In susceptible patients, in particular those with known asthma, more severe falls in FEV_1 could be achieved with this 6-min protocol, and it is for this reason these patients are recommended to be excluded from performing EVH (Weiler et al. 2016). For known asthmatics a 4-min protocol at 21 times the FEV_1 has been used as well as a multistage protocol requiring 3-min periods of ventilation at 10.5, 21, and 31 times FEV_1 (Brannan et al. 1998). If using a multistage protocol in known asthmatic patients, measurements of FEV_1 are made following each EVH stage at 1, 3, 5, and 7 min. If there is no further fall at 7 min, the

subject proceeds to the next level of ventilation. Progressive protocols can induce refractoriness, which leads to an attenuated response at the next ventilation level in some patients. For this reason progressive protocols should not be used routinely. BHR may occur during ventilation, and any sudden falls in ventilation rate could be an indication of bronchoconstriction. In such cases the test may need to cease and FEV_1 be measured immediately, followed by the administration of rescue bronchodilator.

A fall in FEV_1 $\geq$10% from the pre-challenge value is defined as a positive test, and the severity of the fall in FEV_1 defines the severity of the BHR. It is recommended that the fall in FEV_1 should be sustained, with the subject having at least a 10% fall in FEV_1 recorded at two consecutive time points after the challenge (Parsons et al. 2013; Weiler et al. 2016). A fall of 15% has been suggested a more appropriate cutoff value to identify athletes and minimize potential false positives who have a single 10% in FEV_1 post exercise (Price et al. 2016).

EVH has been observed to identify more cases of EIB than laboratory exercise tests, and it is as sensitive as field exercise testing for athletes (Dickinson 2006; Mannix et al. 1999; Rundell et al. 2004b). This is likely due to the higher levels of ventilation that can be rapidly achieved and sustained using EVH compared with laboratory exercise on a bicycle or treadmill. Thus, persons with mild EIB with a negative response to an exercise protocol may have a positive response to the 6-min dry air EVH protocol. Assessments of the reproducibility of the airway response to EVH are limited to small populations of either athletes or nonathletes (Stadelmann et al. 2011; Price et al. 2015; Argyros et al. 1996; Williams et al. 2015). Variations around the diagnostic cutoff value of 10% with mild BHR occur, similar to the observed variations with exercise (Anderson et al. 2010), suggesting the possible need for two tests in borderline responses if EIB is still suspected (Weiler et al. 2016; Price et al. 2016). Those with moderate falls in FEV_1 to EVH appear to have adequate reproducible airway responses over 3 and 6 weeks (Argyros et al. 1996; Williams et al. 2015).

17.4.4 Inhaled Mannitol

The mannitol challenge test was developed in an attempt to make an indirect BPT more clinically accessible, so the test could move beyond the clinical laboratory to be performed safely in a clinical office setting (Anderson et al. 2018). Prior to development of mannitol, osmotic challenge testing was performed using aerosols of hypertonic saline generated by large volume ultrasonic nebulizers that were confined to clinical laboratories (Anderson and Brannan 2003). There were additional disadvantages with nebulization, such as variation in the delivered dose of aerosol, hygienic problems related to the patient expiration of the wet aerosols and exposure of technical staff, as well as the requirement to regularly clean and maintain equipment. Mannitol dry powder produced using spray drying in order to provide a uniform particle size was found to be stable and suitable for encapsulation (Anderson et al. 1997). The pre-prepared package of mannitol provides a common operating standard for BPTs with potential to compare results in different laboratories.

Following the establishment of reproducible baseline spirometry, the mannitol test requires the patient to inhale increasing doses of dry powder mannitol and has the FEV_1 measured in duplicate 60 s after each dose. The FEV_1 at each dose step should be within repeatable values within 5%. The test protocol consists of 0 mg (empty capsule), 5, 10, 20, 40, 80 mg (2 $\times$ 40 mg capsules), and three doses of 160 mg (4 $\times$ 40 mg capsules) of mannitol. The maximum cumulative dose of mannitol that is administered is 635 mg (Brannan et al. 2005).

A positive test result is defined as either a fall in FEV_1 of 15% from baseline (i.e., post 0-mg capsule) or a 10% fall in FEV_1 from baseline between two consecutive doses (Brannan et al. 2005). If a patient presenting with symptoms suggestive of EIB has a fall of greater than 10% but less than 15% following the maximum cumulative dose of 635 mg (i.e., only documenting a PD_{10}), then mild EIB could be considered (Holzer et al. 2003) (Fig. 7).

The mannitol test needs to be performed in a timely manner so that the osmotic gradient is

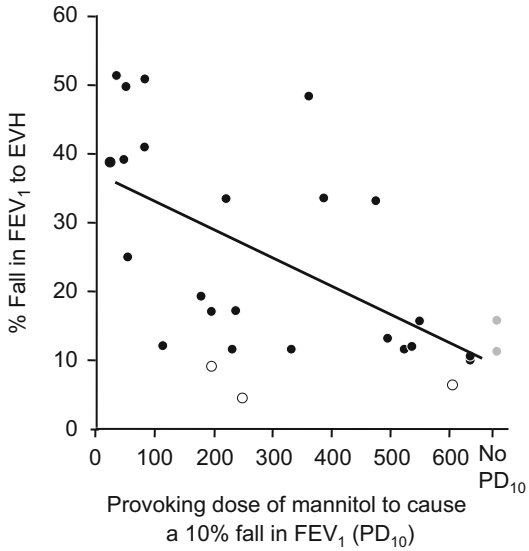


Fig. 7 In elite athletes, the relationship of the airway response to eucapnic voluntary hyperpnea (EVH) expressed as a percent fall in FEV_1 and the airway response to mannitol expressed as the cumulative dose to cause a 10% fall in FEV_1 (PD_{10}). The majority who responded to both tests (black dots) with those positive to EVH alone (gray dots) and those responsive to mannitol alone (white dots). In 24 subjects who had airway responses to both tests, there was a good relationship between percent fall in FEV_1 to EVH and the PD_{10} to mannitol ($r_p = 0.61$, $r_s = 0.70$, $p < 0.01$). (Reproduced with permission from (Holzer et al. 2003))

increased with each dose. The repeatability of the PD_{15} to mannitol is one doubling dose using a low-resistance dry powder inhaler (Anderson et al. 1997; Brannan et al. 2001). The time to complete a positive test as observed in a large phase 3 trial was 17 min (±7 min) for a positive test and 26 min (±6 min) for a negative test (Anderson et al. 2009).

It was also found that a test taking more than 35 min may lead to a false-negative result. Excessive cough may be a reason for delaying the duration of the challenge test; however, it has been demonstrated excessive cough to mannitol may indicate cough hypersensitivity syndrome (Koskela et al. 2018).

Inhaled mannitol has demonstrated adequate safety both in established phase 3 trials and in the field in epidemiology studies (Anderson et al. 2009; Brannan et al. 2005; de Menezes et al. 2018). Airway responses are reversed rapidly with a standard dose of bronchodilator (Brannan et al. 2005; Anderson et al. 1997). Not unlike that observed with other BPTs, prolonged recovery to a standard dose of bronchodilator can be observed in patients who use beta2-agonists regularly, which may be indicative of tolerance to beta2-agonist use (Haney and Hancox 2006). It is also becoming clearer that BHR to mannitol may be more sensitive than a laboratory exercise challenge. Mannitol has also been shown to identify BHR 1.4 times more than a 10% fall in FEV_1 to laboratory running exercise and 1.65 times more if a 15% fall to exercise is considered as an abnormal response in persons with newly diagnosed asthma (Anderson et al. 2009). Mannitol is also more sensitive at identifying BHR compared to a laboratory cycle exercise in known asthmatic individuals (Seccombe et al. 2018).

17.5 Therapy for Exercised-Induced Bronchoconstriction

EIB in those with asthma, even in the presence of minimal daily symptoms, may represent inadequacy of control of asthma (National Asthma Education and Prevention Program 2007; Global Initiative for Asthma 2007b). The goal of therapy for EIB in a person with asthma is to prevent symptoms induced by exercise while enhancing overall control of asthma. Pharmacotherapeutic agents that are useful in controlling chronic asthma usually have bronchoprotective activity for EIB as well. If asthma is otherwise well controlled, bronchoprotective therapy for EIB is administered only as needed, or in cases of optimal anti-inflammatory, bronchoprotective therapy for EIB may not be required. Considering this it should be noted that exercise symptoms may be one of the last manifestations of asthma that will resolve with routine longer-term treatment strategies.

Therapy for EIB may be delivered by inhalation or by oral administration minutes to hours before exercise, respectively. However, in general, acute treatments via the inhaled route provide

more rapid bronchoprotective effects. When used alone or in combination with pharmacotherapy, nonpharmacological therapies can also be helpful in preventing EIB. Pharmacological agents act to prevent or attenuate EIB often by different mechanisms and different degrees of protection among different individuals. No therapies when given acutely can be guaranteed to completely eliminate EIB. However, the attenuation of EIB minimizes bronchospasm during exercise and reduces the severity of the response following exercise (Rossing et al. 1982; Latimer et al. 1983).

Changes in airway responsiveness over time, environmental conditions, intensity of the exercise stimulus, and the frequency of use of existing asthma therapies may lead to the variability of effectiveness of treatments within an individual (Guidance for Industry 2002). The variability observed with different treatments may also result from differences in baseline airway responsiveness and susceptibility of tolerance to a specific treatment (Anderson et al. 2006). The most common and standardized primary end point for assessing the efficacy of a drug in the treatment of EIB either in a clinical trial or in clinical practice is the maximum percentage fall in FEV_1 (Guidance for Industry 2002). In addition to this maximum absolute fall in FEV_1, expressed as a percentage of baseline, the results may indicate a change in the percent fall in FEV_1 before and after either acute or long-term therapy. The percent protection for a drug on EIB can be determined permitting a comparison of efficacy between treatments (Kemp et al. 1998).

17.5.1 Pharmacological Therapy

The most effective therapeutic class for acute prevention of intermittent EIB are beta2-adrenergic receptor agonists (Spooner et al. 2003). For most patients they provide the best protection against EIB (Anderson et al. 1991, 2001; Spooner et al. 2003; Hendrickson et al. 1994; Ferrari et al. 2000, 2002; Bisgaard 2000). Alternatively, when administered following bronchoconstriction to exercise, they enhance recovery of FEV_1 to baseline values (Anderson et al. 1979; Godfrey and Konig 1975b). When inhaled between 5 and 20 min before exercise, SABA drugs which were initially developed for asthma were highly effective in protecting against EIB, as shown in early investigations (Anderson et al. 1976; Hendrickson et al. 1994; Godfrey and Konig 1976; McFadden and Gilbert 1994). This protection, however, does not occur when beta2-agonists are given in an oral formulation suggesting they must be administered topically to the airway surface (Anderson et al. 1976). The bronchoprotective effect lasts 2–4 h after inhalation, and there are no significant differences among the different SABAs currently in use, such as albuterol and terbutaline (Anderson et al. 1991; Woolley et al. 1990). The cromolyn drugs that are mast cell stabilizers have been used as add-on therapy to enhance SABAs in increasing bronchoprotection; however, it is important to recognize that part of the superior action of beta2-agonists is to also stabilize mast cells (Spooner et al. 2003; Tan and Spector 2002).

There are now a number of long-acting beta2-agonists (LABAs) in use. Many of the new LABAs (but none of the ultra-LABAs) have currently been formally assessed for their efficacy to inhibit EIB. LABAs differ in their actions, mainly in their onsets of effect. Salmeterol requires up to 30 min for its optimal action to take effect. In contrast, formoterol has a rapid onset of bronchodilator and bronchoprotective action similar to SABAs (Ferrari et al. 2000, 2002). In beta2-agonist-naïve patients, prolonged (up to 12 h) duration of bronchoprotective effect has been shown for these drugs after the first dose (Anderson et al. 1991; Bisgaard 2000; Kemp et al. 1994; Nelson et al. 1998; Carlsen et al. 1995; Newnham et al. 1993). Many patients are not protected for this entire dosing interval. The optimal dosing interval for EIB bronchoprotection may be closer to 6 h on average (Anderson et al. 1991; Kemp et al. 1994; Nelson et al. 1998; Newnham et al. 1993).

LABAs provide prolonged, sustained protection with intermittent use (Kemp et al. 1994; Newnham et al. 1993; Boner et al. 1994; Vilsvik et al. 2001; Bronsky et al. 2002), but daily maintenance use of LABAs (and SABAs) can result in "tolerance," i.e., some loss of bronchoprotection,

with cross-tolerance to other beta2-agonists (Nelson et al. 1998; Ramage et al. 1994; Simons et al. 1997; Haney and Hancox 2005; Villaran et al. 1999; Edelman et al. 2000; Hancox et al. 2002; Inman and O'Byrne 1996). Moreover, the severity of EIB may actually increase with daily use of LABAs and SABAs (Hancox et al. 2002; Inman and O'Byrne 1996). It is well established that regular beta2-agonists can increase BHR to both direct and indirect stimuli, suggesting regular beta2 stimulation can increase airway smooth muscle sensitivity (Haney and Hancox 2006). Further, the degree of tolerance may increase with increasing bronchoconstriction which could potentially put patients with severe asthma attacks at risk of experiencing even less bronchodilator responsiveness (Wraight et al. 2003). Therefore, adrenergic agonists are recommended for only intermittent use for bronchoprotection (Parsons et al. 2013; Weiler et al. 2007). Tolerance occurs in most patients who demonstrate EIB (Haney and Hancox 2005; Hancox et al. 2002; Inman and O'Byrne 1996; Wraight et al. 2003; Hancox et al. 1999, 2000; Haney and Hancox 2007); however, some individuals may have a greater propensity than others to develop tolerance. To assess if there was a genetic basis to beta2-agonist tolerance, patients with and without the Arg16Gly beta2-receptor polymorphism, which previously suggested a susceptibility to beta2-agonist tolerance, demonstrated that these polymorphisms do not influence tolerance to loss of bronchoprotection to beta2-agonists with EIB (Bonini et al. 2013). Notably, tolerance occurs even when patients are also receiving ICS suggesting attenuating airway inflammation is independent of the mechanism of beta2-receptor tolerance (Weiler et al. 2005; Simons et al. 1997).

Tolerance is demonstrated most noticeably by a decrease in protective effect of both SABA (Storms et al. 2004) and LABA (Weiler et al. 2005; Bisgaard 2000; Nelson et al. 1998; Boner et al. 1994; Simons et al. 1997) (Fig. 8). This tolerance has been demonstrated in one study to occur in less than 3 h (Garcia et al. 2001). In addition, tolerance manifests by prolongation of recovery from bronchoconstriction with a standard dose of rescue beta2-agonist (Haney and Hancox 2005; Hancox et al. 2002). It is possible that the presence of tolerance is often missed in a clinical setting because a patient rarely is evaluated for responsiveness to bronchodilator following bronchospasm. Thus, the shorter duration of bronchoprotection and prolonged recovery time can go unreported without objective measurement. Prescribing additional doses of SABA before exercise in an asthmatic patient taking intermittent to regular beta2-agonists for daily symptom control may unintentionally contribute to potential worsening of beta2-agonist tolerance.

The mechanisms by which regular long-term beta2-agonist use causes tolerance to acute use of beta2-agonist are not completely understood, but beta2-agonists can increase smooth muscle sensitivity (Haney and Hancox 2006; Anderson et al. 2006). Another possible explanation is that the long-term exposure of beta-receptors to beta2-agonists results in uncoupling and internalization or sequestration in the cells (Johnson 2006). "Downregulation" of receptors and decreasing responsiveness to beta2-agonists result from the net loss in the number of available functional beta2-receptors (Hayes et al. 1996) which manifests as an absence of optimal clinical protection to bronchoconstrictive stimuli. Thus, resynthesis of the receptor to the active state is required for restoration of sensitivity. Within 72 h of cessation of exposure to beta2-agonist, the restoration of sensitivity is observed clinically (Haney and Hancox 2005; Davis et al. 2003b).

Mediator release from mast cells is inhibited using beta2-agonists by stimulation by beta-receptors on the cell surface. The process of beta2-receptor desensitization varies between bronchial mast cells, which appear to be more readily desensitized when compared to bronchial smooth muscle cells, which have larger numbers of beta2-receptors (Johnson 2006; McGraw and Liggett 1997; Chong et al. 2003; Scola et al. 2004). The clinical effects of downregulation on mast cells are related more to bronchoprotection, than to smooth muscle and bronchodilation (O'Connor et al. 1992). It is also possible the downregulation of mast cell beta2-receptors could have a dual effect, boosting mediator release and increasing bronchoconstriction

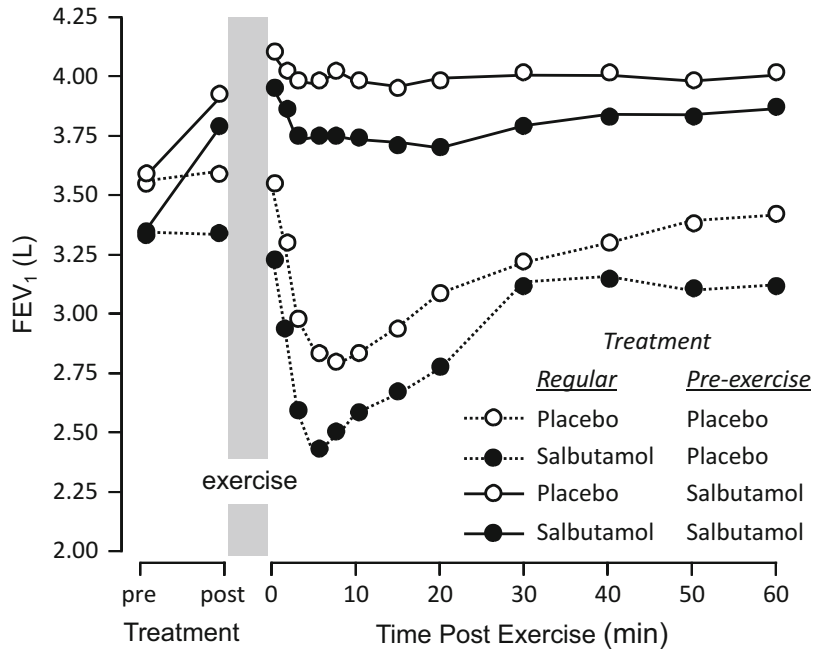


Fig. 8 Mean forced expiratory volume in 1 s (FEV_1) before and following a pre-exercise dose of 200 mcg of salbutamol or placebo followed by 5 min of constant workload exercise on a cycle ergometer in asthmatics with EIB. Exercise tests followed 7 days of regular treatment of 800 mcg per day of salbutamol and placebo. One week of regular treatment with salbutamol resulted in a decrease in baseline FEV_1, more marked EIB, and decreased protective effect of salbutamol on EIB. (Reproduced with permission from (Inman and O'Byrne 1996))

(Hancox et al. 2002; Chong et al. 2003; Scola et al. 2004; Swystun et al. 2000; Peachell 2006).

Beta2-receptor downregulation, or tolerance, is exhibited clinically as a decrease in duration of beta2-agonist bronchoprotection to stimuli such as exercise, which depends on mast cell mediator release for bronchoconstriction (Anderson et al. 2006). Tolerance to bronchodilation following EIB is shown by protraction of the time of recovery from bronchoconstriction in response to usual doses of beta2-agonists (Haney and Hancox 2005; Hancox et al. 2002; Inman and O'Byrne 1996).

Daily monotherapy use of LABAs to provide overall asthma control is not recommended (National Asthma Education and Prevention Program 2007). LABAs are often combined with ICS to provide effective maintenance therapy when ICS alone are not satisfactory in controlling chronic asthma; however, there is no persuasive clinical evidence that this combination reduces tolerance to the bronchoprotective effect of LABAs in asthma or EIB with asthma (Weiler et al. 2005; Simons et al. 1997; Kalra et al. 1996). LABAs alone, used intermittently up to three times a week, do not appear to be connected with tolerance (Davis et al. 2003b; FDA drug safety communication 2010).

Although their role appears to vary significantly among patients, leukotrienes in EIB sustain the bronchoconstrictive and inflammatory response. Inhibitors of the leukotriene pathway (leukotriene receptor antagonists or LTRAs and lipoxygenase inhibitors) are not only effective in enhancing recovery of airway narrowing but also reducing the severity of the fall in FEV_1. However, a limitation may be the variability in the effectiveness of LTRAs, from completely blocking EIB in some asthmatic individuals to little or no bronchoprotection at all in some individuals. However, most patients do not experience comprehensive protection (Raissy et al. 2008). Approximately 50% of patients can respond to these treatments, with a 30–80% protection of EIB (Kemp et al. 1998; Stelmach et al. 2008; Vidal et al. 2001). These percentages may differ, contingent in part on the FEV_1 fall required to make a diagnosis of EIB (>10%, >15%, or > 20%). Given that other mediators (e.g., PGD_2, histamine) (Hallstrand et al. 2005b; Finnerty and Holgate 1990) are involved in EIB, this incomplete protection is perhaps not surprising.

Several LTRAs have been found to be effective in reducing EIB (Leff et al. 1998; O'Byrne 2000;

Pearlman et al. 1999; Manning et al. 1990; Finnerty et al. 1992) (Fig. 9). Most studies have examined the $CystLT_1$ receptor antagonist, particularly montelukast, and zafirlukast and pranlukast can be used as well. Montelukast is approved by the FDA and many other health-care regulatory authorities worldwide for treatment of EIB in children, adolescents, and adults. As it is an oral formulation, its onset of action is not as fast as an inhaled treatment that can acutely protect against EIB. Montelukast has an onset of action within 1–2 h of oral administration (Pearlman et al. 2006; Finnerty et al. 1992; Philip et al. 2007a; Wasfi et al. 2011) but provides a duration of bronchoprotection for at least 24 h (Leff et al. 1998; Pearlman et al. 2006; Kemp et al. 1998; Wasfi et al. 2011; Philip et al. 2007b; Bronsky et al. 1997). It should be noted that maximum protection may not be maintained in some patients (Peroni et al. 2002a). LTRAs also speed the time to recovery to baseline lung function following EIB (Leff et al. 1998; Storms et al. 2004). While LTRAs do not have the same effectiveness overall in attenuating EIB as rapidly as beta2-agonists (Raissy et al. 2008), tolerance has not been observed with $CystLT_1$ antagonists with long-term use (Leff et al. 1998; Villaran et al. 1999; Edelman et al. 2000; de Benedictis et al. 2006). Populations of responders and nonresponders of leukotriene antagonists to EIB have been observed similar to that observed for these drugs on asthma control to daily symptoms (Drazen et al. 2000; Kang et al. 2008; Kim et al. 2008).

Lipoxygenase inhibitors, a second group of agents that affect the leukotriene pathway by inhibiting synthesis, are less widely used in the treatment of EIB and are not currently recommended for this indication. While lipoxygenase inhibitors have been shown to attenuate EIB when given orally (Meltzer et al. 1996; Coreno et al. 2000; Lehnigk et al. 1998; van Schoor et al. 1997), the duration of inhibition of these compounds is relatively short (Meltzer et al. 1996; Coreno et al. 2000). Early stage development studies suggest a 5-lipoxygenase activating protein (FLAP) inhibitor that can target different stages of the leukotriene synthesis pathway and can inhibit EIB (Kent et al. 2014).

Mast cell stabilizers such as cromolyn sodium and nedocromil sodium (not currently available as an MDI or DPI in the United States), two structurally unrelated compounds, have no bronchodilator action but have similar bronchoprotective action against EIB when inhaled (Spooner et al.

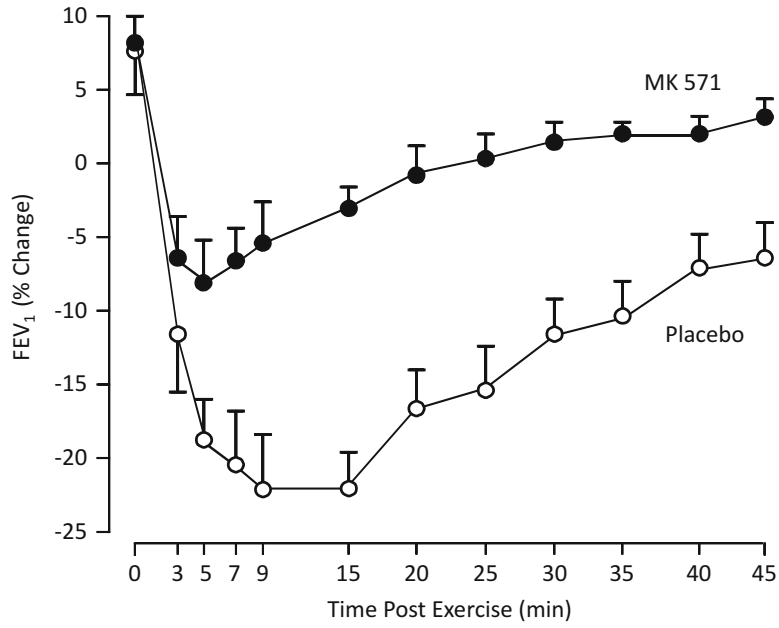


Fig. 9 The first evidence to demonstrate in asthmatics that the leukotriene receptor antagonist MK-571 (eventually known as montelukast) administered intravenously inhibits EIB by attenuating the reduction in forced expiratory volume in 1 s (FEV_1) following exercise and causing rapid recovery to pre-exercise FEV_1 values. (Reproduced with permission from (Manning et al. 1990))

2003; Kelly et al. 2001). A number of mechanisms have been suggested for these agents, including inhibition of mast cell mediator release of PGD_2 (Kippelen et al. 2010a; Brannan et al. 2006). The bronchoprotective effect is of short duration (1–2 h) (Woolley et al. 1990; Comis et al. 1993), but bronchoprotection is immediate, suggesting activity occurs on or close to the airway epithelium (Silverman and Andrea 1972). Further, these agents may be effective and may increase overall inhibition of EIB when combined with other drugs used to diminish EIB (Spooner et al. 2003; McFadden and Gilbert 1994; Comis et al. 1993; de Benedictis et al. 1998). Similar to other treatments for EIB, there is significant intersubject and between-study variability on bronchoprotection (Tullett et al. 1985; Patel and Wall 1986). The effectiveness of cromolyn appears to be dose related; however, while these drugs have few side effects, they may have been administered in insufficient doses (Patel and Wall 1986; Schoeffel et al. 1983; Patel et al. 1986). There is no evidence of tolerance with the cromolyn drugs. Due to observed safety profiles and rapid onset of action, these agents have been regularly used to attenuate EIB (Spooner et al. 2003; Kuzemko 1989).

In asthmatic patients EIB is best controlled by maintenance anti-inflammatory treatment using ICS (Subbarao et al. 2006; Hofstra et al. 2000; Jonasson et al. 2000) or in combination with other short-term preventive treatment (National Asthma Education and Prevention Program 2007; Stelmach et al. 2008; National Institutes of Health NH, Lung and Blood Institute 2007). ICS are the mainstay therapy for the improvement in asthma control in the majority of patients with persistent asthma symptoms; however, it is also effective at attenuating BHR to both direct and indirect stimuli, including exercise (Anderson and Holzer 2000; Brannan 2010). Adherence to ICS should be encouraged for the treatment of EIB, as it should be encouraged for the routine management of asthma. The dose-dependent effect of ICS has been noted shortly following the initial 3–4 weeks of treatment (Subbarao et al. 2006; Pedersen and Hansen 1995). The effects of ICS are time dependent, however, with longer treatment periods (12 weeks) showing no difference between different doses of ICS inhibiting EIB (Jonasson et al. 2000). There is no relationship between control of persistent asthma and severity of EIB (Madhuban et al. 2011). Nevertheless, the presence of EIB in the presence of regular ICS can be considered a reflection of the lack of pathophysiological control of asthma, even in the presence of good clinical control. In this case, if moderate to severe EIB is present with minimal symptoms suggestive of adequate asthma control, this should suggest a need to maintain therapy.

The mechanism of regular ICS may be different when administered acutely. Bronchoprotection against EIB with acute high-dose ICS has been documented as early as 4 h after the first dose in adults (Kippelen et al. 2010c; Thio et al. 2001; Driessen et al. 2011). In children, however, it has been demonstrated that lower doses consistent with the daily treatment of asthma can have a more immediate bronchoprotective effect on EIB (Visser et al. 2014). The mechanisms are unclear but possibly similar to other inhaled treatments by impacting epithelial function. After 1 week of ICS treatment, efficacy appears to plateau in studies of short treatment duration (Duong et al. 2008; Subbarao et al. 2006; Pedersen and Hansen 1995). However, bronchoprotection may increase further over weeks or even months until it reaches its final plateau, which may exist in the form of complete bronchoprotection (Koh et al. 2007; Hofstra et al. 2000; Henriksen and Wenzel 1984; Henriksen 1985) (Fig. 10). Bronchoprotection with regular ICS has been demonstrated to occur in 30–60% of asthmatic patients with EIB, with marked individual variability that can range from complete inhibition of EIB to minimal protection (Koh et al. 2007). It has yet to be determined if an individual who does not benefit from attenuated EIB with regular ICS is corticosteroid insensitive or poorly adherent to treatment. Without studies understanding the duration of effect of ICS on EIB and accounting for adherence to ICS, it will remain unclear whether this variability reflects distinct subpopulations of ICS responders and nonresponders (e.g., a reflection of genetic differences) or if this is a feature of the severity of EIB.

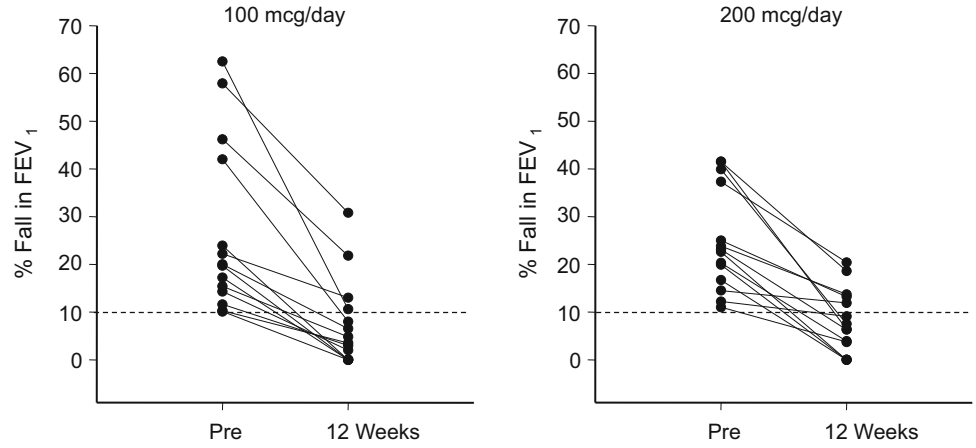


Fig. 10 Individual data of the effect of 12 weeks of treatment with low doses of inhaled corticosteroid (ICS) budesonide (100 mcg or 200 mcg, once daily) on the percentage fall in FEV_1 in children with asthma who have EIB. The majority of children were observed to have a negative exercise challenge test (<10% fall in FEV_1) with 71% (10 of 14) and 64% (9 of 14) following 100 mcg or 200 mcg, respectively. The data demonstrates that it is possible to treat with regular ICS over a longer time period and see resolution in airway sensitivity to an exercise challenge, independent of dose of ICS. (Reproduced with permission from (Jonasson et al. 1998))

Allergic rhinitis can be common in atopic asthmatic patients, and some evidence suggests that effective treatment of nasal congestion and obstruction by nasal ICS is related to at least mild protection of EIB (Henriksen and Wenzel 1984; Kersten et al. 2012; Shturman-Ellstein et al. 1978). These findings appear to validate the "unified airway" theory that considers allergic rhinitis and atopic airway inflammation in asthma are demonstrations of similar pathologic processes throughout the respiratory tract (Brozek et al. 2010). This suggests that treating EIB with both intranasal corticosteroids and ICS could lead to more effective attenuation of EIB in allergic asthmatics compared to ICS alone, however, as yet there is no evidence to support this conclusion.

As daily treatment with ICS may not completely inhibit EIB, this does not remove the need for acute bronchoprotection for EIB to aid for more complete protection. Beta2-agonists can be added when the need is required for additional short-term protection of EIB (Anderson et al. 1979; Godfrey and Konig 1975b). As an alternative, and considering beta2-agonist tolerance could be an issue, when maintenance ICS are not effective enough, LTRAs can be used to obtain added protection with low- and medium-dose ICS (Stelmach et al. 2008; Duong et al. 2012) while also using beta2-agonists for acute bronchoprotection if necessary (Fitch et al. 2008; Global Initiative for Asthma 2007b; Grzelewski and Stelmach 2009; Carlsen et al. 2008b).

The evidence shows little improvement by ICS of tolerance to beta2-agonist bronchoprotection, and a shortened duration of bronchoprotection remains when ICS and LABAs are given together (Weiler et al. 2005; Simons et al. 1997; Storms et al. 2004; Kalra et al. 1996; Yates et al. 1996). Nonetheless, one study that evaluated the combination of an ICS and LABA (fluticasone and salmeterol) for four weeks of maintenance therapy in adult patients showed better bronchoprotection at 1 and 8.5 h after dosing compared with the same dose of monotherapy fluticasone (Weiler et al. 2005). In that study, most patients taking the combined therapy also exhibited greater complete protection (<10% fall of FEV_1) and better overall asthma control. A similar study with the same agents in children and adolescents also demonstrated a small persistent effect of bronchoprotection when the combination was used compared with the monotherapy ICS (Pearlman et al. 2009). EIB is reduced by a similar magnitude over 6 weeks when comparing LABAs

in combination with ICS versus a low dose of ICS daily (Lazarinis et al. 2014).

Anticholinergic agents act to cause bronchodilation by blocking vagally mediated tone and have been used alone and in combination with SABAs with some success in treating acute exacerbations of asthma (Knopfli et al. 2005; Blake 2006). In double-blind trials, especially with placebo controls, the ability of anticholinergic agents to prevent EIB has not been consistent (Boulet et al. 1989). Not all patients seem to respond to anticholinergic agents (Spooner et al. 2003; de Benedictis et al. 1998; Poppius et al. 1986; Magnussen et al. 1992), and responsiveness may be variable within the same patient (Boner et al. 1989). There is no evidence to suggest these drugs would be useful in combination, and there is no study to date assessing any of the longer acting anticholinergics in EIB.

The methylxanthines theophylline and aminophylline have been used for long-term maintenance therapy in the treatment of asthma, and these agents have been used as adjunct therapy to ICS when an additional agent is required to improve asthma control (Global Initiative for Asthma 2007b; National Institutes of Health NH, Lung and Blood Institute 2007). The methylxanthines are nonselective phosphodiesterase inhibitors of the cyclic AMP and cyclic guanine monophosphate pathways active in the pathophysiology of asthma. Methylxanthines have been shown to modify EIB in only a subset of patients with EIB (Ellis 1984; Iikura et al. 1996; Seale et al. 1977). Selective phosphodiesterase inhibitors have a better safety profile than methylxanthines with one study using the phosphodiesterase 4 inhibitor, roflumilast, showing attenuation of EIB (Timmer et al. 2002).

The methylxanthine drug class also includes caffeine. Ingestion of caffeine can attenuate EIB in a dose response manner, with evidence of high doses of caffeine (6–10 mg/kg) inhibiting EIB (Duffy and Phillips 1991; Kivity et al. 1990; VanHaitsma et al. 2010). The recommendation to abstain from caffeine prior to performing BPTs to identify EIB is based on these studies (Weiler et al. 2016).

Antihistamines or H_1 antagonists can provide incomplete attenuation of EIB (Patel 1984; Baki and Orhan 2002; Finnerty and Holgate 1990; Clee et al. 1984; Magnussen et al. 1988; Wiebicke et al. 1988; Zielinski and Chodosowska 1977), but results have been inconsistent (Dahlén et al. 2002; Peroni et al. 2002b). This variability may relate to variances in the intensity and duration of the exercise stimulus, the severity of the EIB in the population studied, or the specific dose of the antihistamine. The antihistamine class is pharmacodynamically diverse as well. Greater intensity or more severe EIB may be required for participation of histamine in the pathogenesis of EIB (Anderson and Brannan 2002). Histamine is also less potent than the other two main mediators (leukotrienes and prostaglandins) that contribute to EIB (O'Byrne 1997). Antihistamines may have other actions such as an ability to inhibit mediator activation and release (Passalacqua et al. 2002). Dissimilar routes of administration and dosages of antihistamines may also be confounding factors in previous studies (Ghosh et al. 1991). The evidence to date suggests the effectiveness of oral antihistamines should not be considered a treatment to aid in the effective inhibition of EIB. Considering this, it will likely remain as a treatment option in allergic rhinitis in the hope that there will be some additional benefits in those with comorbid asthma and EIB.

Additional considerations to the management of EIB in elite athletes should include moderating relevant environmental exposures as much as possible (such as methods to reduce home or occupational allergen exposures, minimizing air pollution exposure), treating comorbid conditions that may have additional impacts on dyspnea, and patient education (Fitch et al. 2008; Boulet and O'Byrne 2015). The athlete and the specialist may need to consider an exercise prescription that has additional considerations such as the athlete's routine and exercise environment in order to provide adequate control of EIB (e.g., swimmers, ice hockey players).

It should be noted that similar to observations in asthmatic patients with EIB, the few studies in athletes with EIB alone have shown the same results for the acute protective effect of a beta2-

agonist, the mast cell stabilizer cromoglycate, the LTRA montelukast, and the inhibitory effect of high-dose ICS when given acutely (Kippelen et al. 2010a, c; Simpson et al. 2013; Rundell et al. 2005). These findings reinforce the concept that similar pathophysiological mechanisms occur in EIB with or without the daily symptoms of asthma.

17.5.2 Nonpharmacological Therapy and Dietary Modification

For some athletes, continuous warm-up before exercise has been shown to cause significant decrease in post-exercise bronchoconstriction (Stickland et al. 2012). The precise mechanisms for an about 50% reduction in airway responsiveness in 50% of persons with EIB with repeated exercise following an initial exercise stimulus are not well understood. Pre-exercise warm-up is not a useful treatment option in all patients, and there are currently no predictors of the response other than to objectively measure attenuated EIB after repeated exercise separated by 60–90 min. Pre-exercise warm-up at 60–80% maximum heart rate can be performed to provide partial attenuation of EIB for up to 4 h (Edmunds et al. 1978; Schoeffel et al. 1980; Anderson and Schoeffel 1982). Due to the incomplete protection, pre-exercise warm-up does not prevent the need for pharmacotherapy. Combination of pharmacotherapy and warm-up should be considered as it has been shown that SABA plus a warm-up gives better protection than the warm-up or SABA alone (Mickleborough et al. 2007; McKenzie et al. 1994).

Dietary modification as a treatment for EIB has generally been used as evidence of significant yet partial inhibition of the percent fall in FEV_1 following exercise with low-salt diets, omega-3 fatty acids, and ascorbic acid (vitamin C) with up to 3 weeks of modification (Mickleborough et al. 2001, 2003, 2005, 2006; Tecklenburg et al. 2007). If dietary supplementations are to be prescribed, they should not be seen as a substitute for established pharmacotherapies but should be used in association with maintenance therapy in the asthmatic athlete.

17.6 Conclusion

Asthma in athletes can have significant implications for exercise performance by causing EIB. For optimal treatment of EIB, it is important to have the presence and severity of EIB characterized using a standardized BPT that causes BHR via the release of bronchoconstricting mediators. Indirect tests are useful not only for identifying an airway that is sensitive to the treatments used in asthma, in particular ICS, but also to assess the efficacy of therapy after treatment. Understanding the advantages and disadvantages of the treatments and strategies for EIB can help diminish EIB while also aiding in the treatment of asthma. The optimal point to treatment in the asthmatic athlete is the significant attenuation and, if possible, the abolition of EIB. Based on the evidence of clinical trials, this attenuation and/or abolition would lead to improvements in exercise performance while significantly minimizing the likelihood for an attack of asthma with exercise.

References

Aitken ML, Marini JJ. Effect of heat delivery and extraction on airway conductance in normal and in asthmatic subjects. Am Rev Respir Dis. 1985;131:357–61.

Anderson SD. Asthma provoked by exercise, hyperventilation, and the inhalation of non-isotonic aerosols. In: Barnes PJ, Rodger IW, Thomson NC, editors. Asthma: basic mechanisms and clinical management. 2nd ed. London: Academic; 1992. p. 473–90.

Anderson SD. Indirect challenge tests: airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest. 2010;138(2 Suppl):25S–30S.

Anderson SD. 'Indirect' challenges from science to clinical practice. Eur Clin Respir J. 2016;3:31096.

Anderson SD, Brannan JD. Exercise induced asthma: is there still a case for histamine? (editorial). J Allergy Clin Immunol. 2002;109(5 Pt 1):771–3.

Anderson SD, Brannan JD. Methods for 'indirect' challenge tests including exercise, eucapnic voluntary hyperpnea and hypertonic aerosols. Clin Rev Allergy Immunol. 2003;24:63–90.

Anderson SD, Daviskas E. The airway microvasculature and exercise-induced asthma. Thorax. 1992;47:748–52.

Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is …. J Allergy Clin Immunol. 2000;106(3):453–9.

Anderson SD, Holzer K. Exercise-induced asthma: is it the right diagnosis in elite athletes? J Allergy Clin Immunol. 2000;106(3):419–28.

Anderson SD, Kippelen P. Exercise-induced bronchoconstriction: pathogenesis. Curr Allergy Asthma Rep. 2005;5:116–22.

Anderson SD, Kippelen P. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. J Allergy Clin Immunol. 2008;122:225–35.

Anderson SD, Kippelen P. Assessment of EIB: what you need to know to optimize test results. Immunol Allergy Clin N Am. 2013;33(3):363–80, viii.

Anderson SD, Schoeffel RE. Respiratory heat and water loss during exercise in patients with asthma: effect of repeated exercise challenge. Eur J Respir Dis. 1982;63:472–80.

Anderson SD, Seale JP, Rozea P, Bandler L, Theobald G, Lindsay DA. Inhaled and oral salbutamol in exercise-induced asthma. Am Rev Respir Dis. 1976;114:493–500.

Anderson SD, Seale JP, Ferris L, Schoeffel RE, Lindsay DA. An evaluation of pharmacotherapy for exercise-induced asthma. J Allergy Clin Immunol. 1979;64:612–24.

Anderson SD, Bye PTP, Schoeffel RE, Seale JP, Taylor KM, Ferris L. Arterial plasma histamine levels at rest, during and after exercise in patients with asthma: effects of terbutaline aerosol. Thorax. 1981;36:259–67.

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

Anderson SD, Brannan J, Spring J, Spalding N, Rodwell LT, Chan K, et al. A new method for bronchial-provocation testing in asthmatic subjects using a dry powder of mannitol. Am J Respir Crit Care Med. 1997;156:758–65.

Anderson SD, Lambert S, Brannan JD, Wood RJ, Koskela H, Morton AR, et al. Laboratory protocol for exercise asthma to evaluate salbutamol given by two devices. Med Sci Sports Exerc. 2001;33(6):893–900.

Anderson SD, Fitch K, Perry CP, Sue-Chu M, Crapo R, McKenzie D, et al. Responses to bronchial challenge submitted for approval to use inhaled beta2 agonists prior to an event at the 2002 Winter Olympics. J Allergy Clin Immunol. 2003;111(1):44–9.

Anderson SD, Caillaud C, Brannan JD. b_2-agonists and exercise-induced asthma. Clin Rev Allergy Immunol. 2006;31(2–3):163–80.

Anderson SD, Charlton B, Weiler JM, Nichols S, Spector SL, Pearlman DS. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Respir Res. 2009;10:4.

Anderson SD, Pearlman DS, Rundell KW, Perry CP, Boushey H, Sorkness CA, et al. Reproducibility of the airway response to an exercise protocol standardized for intensity, duration, and inspired air conditions, in subjects with symptoms suggestive of asthma. Respir Res. 2010;11:120.

Anderson SD, Daviskas E, Brannan JD, Chan HK. Repurposing excipients as active inhalation agents: the mannitol story. Adv Drug Deliv Rev. 2018;133:45–56.

Argyros GJ, Phillips YY, Rayburn DB, Rosenthal RR, Jaeger JJ. Water loss without heat flux in exercise-induced bronchospasm. Am Rev Respir Dis. 1993;147:1419–24.

Argyros GJ, Roach JM, Hurwitz KM, Eliasson AH, Phillips YY. Eucapnic voluntary hyperventilation as a bronchoprovocation technique. Development of a standardized dosing schedule in asthmatics. Chest. 1996;109:1520–4.

Aridol™. Mannitol bronchial challenge test website. 2017.

FDA drug safety communication: new safety requirements for long-acting inhaled asthma medications called long-acting Beta-agonists (LABAs). 2010.

Baek HS, Kim YD, Shin JH, Kim JH, Oh JW, Lee HB. Serum leptin and adiponectin levels correlate with exercise-induced bronchoconstriction in children with asthma. Ann Allergy Asthma Immunol. 2011;107(1):14–21.

Baki A, Orhan F. The effect of loratadine in exercise-induced asthma. Arch Dis Child. 2002;86:38–9.

Bardagi S, Agudo A, Gonzalez CA, Romero PV. Prevalence of exercise-induced airway narrowing in schoolchildren from a Mediterranean town. Am Rev Respir Dis. 1993;147:1112–5.

Barreto M, Villa MP, Olita C, Martella S, Ciabattoni G, Montuschi P. 8-Isoprostane in exhaled breath condensate and exercise-induced bronchoconstriction in asthmatic children and adolescents. Chest. 2009;135(1):66–73.

Benarab-Boucherit Y, Mehdioui H, Nedjar F, Delpierre S, Bouchair N, Aberkane A. Prevalence rate of exercise-induced bronchoconstriction in Annaba (Algeria) schoolchildren. J Asthma. 2011;48(5):511–6.

Bernard A, Nickmilder M, Voisin C, Sardella A. Impact of chlorinated swimming pool attendance on the respiratory health of adolescents. Pediatrics. 2009;124(4):1110–8.

Bikov A, Gajdocsi R, Huszar E, Szili B, Lazar Z, Antus B, et al. Exercise increases exhaled breath condensate cysteinyl leukotriene concentration in asthmatic patients. J Asthma. 2010;47(9):1057–62.

Bisgaard H. Long-acting $beta_2$-agonists in management of childhood asthma: a critical review of the literature. Pediatr Pulmonol. 2000;29(3):221–34.

Blake K. Review of guidelines and the literature in the treatment of acute bronchospasm in asthma. Pharmacotherapy. 2006;26(9 Pt 2):148S–55S.

Boner AL, Vallone G, De Stefano G. Effect of inhaled ipratropium bromide on methacholine and exercise provocation in asthmatic children. Pediatr Pulmonol. 1989;6(2):81–5.

Boner AL, Spezia E, Piovesan P, Chiocca E, Maiocchi G. Inhaled formoterol in the prevention of exercise-

induced bronchoconstriction in asthmatic children. Am J Respir Crit Care Med. 1994;149:935–8.

Bonini M, Permaul P, Kulkarni T, Kazani S, Segal A, Sorkness CA, et al. Loss of salmeterol bronchoprotection against exercise in relation to ADRB2 Arg16Gly polymorphism and exhaled nitric oxide. Am J Respir Crit Care Med. 2013;188(12): 1407–12.

Bood JR, Sundblad BM, Delin I, Sjodin M, Larsson K, Anderson SD, et al. Urinary excretion of lipid mediators in response to repeated eucapnic voluntary hyperpnea in asthmatic subjects. J Appl Physiol (1985). 2015;119(3):272–9.

Bougault V, Turmel J, Boulet LP. Bronchial challenges and respiratory symptoms in elite swimmers and winter sport athletes: airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest. 2010;138(2 Suppl):31S–7S.

Boulet LP, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. N Engl J Med. 2015;372(7):641–8.

Boulet L-P, Turcotte H, Tennina S. Comparative efficacy of salbutamol, ipratropium and cromoglycate in the prevention of bronchospasm induced by exercise and hyperosmolar challenges. J Allergy Clin Immunol. 1989;83:882–7.

Brannan JD. Bronchial hyperresponsiveness in the assessment of asthma control: airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest. 2010;138(2 Suppl):11S–7S.

Brannan JD, Porsbjerg C. Testing for exercise-induced bronchoconstriction. Immunol Allergy Clin N Am. 2018;38(2):215–29.

Brannan JD, Koskela H, Anderson SD, Chew N. Responsiveness to mannitol in asthmatic subjects with exercise- and hyperventilation-induced asthma. Am J Respir Crit Care Med. 1998;158(4):1120–6.

Brannan JD, Anderson SD, Gomes K, King GG, Chan H-K, Seale JP. Fexofenadine decreases sensitivity to and montelukast improves recovery from inhaled mannitol. Am J Respir Crit Care Med. 2001;163: 1420–5.

Brannan JD, Gulliksson M, Anderson SD, Chew N, Kumlin M. Evidence of mast cell activation and leukotriene release after mannitol inhalation. Eur Respir J. 2003;22(3):491–6.

Brannan JD, Anderson SD, Perry CP, Freed-Martens R, Lassig AR, Charlton B. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. Respir Res. 2005;6:144.

Brannan JD, Gulliksson M, Anderson SD, Chew N, Seale JP, Kumlin M. Inhibition of mast cell PGD_2 release protects against mannitol-induced airway narrowing. Eur Respir J. 2006;27:944–50.

Bronsky EA, Kemp JP, Zhand J, Guerreiro D, Reiss TF. Dose-related protection of exercise bronchoconstriction by montelukast, a cysteinyl leukotriene-receptor antagonist, at the end of a once-daily dosing interval. Clin Pharmacol Ther. 1997;62(5):556–61.

Bronsky EA, Yegen Ü, Yeh CM, Larsen LV, Della Cioppa G. Formoterol provides long-lasting protection against exercise-induced bronchospasm. Ann Allergy Asthma Immunol. 2002;89:407–12.

Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3):466–76.

Brutsche M, Britschgi D, Dayer E, Tschopp JM. Exercise-induced bronchospasm (EIB) in relation to seasonal and perennial specific IgE in young adults. Allergy. 1995;50(11):905–9.

Cabral ALB, Conceição GM, Fonseca-Guedes CHF, Martins MA. Exercise-induced bronchospasm in children. Am J Respir Crit Care Med. 1999;159:1819–23.

Carlsen KH, Roksund O, Olsholt K, Nija F, Leegard J, Bratten G. Overnight protection by inhaled salmeterol on exercise-induced asthma in children. Eur Respir J. 1995;8:1852–5.

Carlsen KH, Engh G, Mørk M. Exercise induced bronchoconstriction depends on exercise load. Respir Med. 2000;94(8):750–5.

Carlsen KH, 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 I 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. 2008a;63(4):387–403.

Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, et al. Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2)LEN. Allergy. 2008b;63(5): 492–505.

Carraro S, Corradi M, Zanconato S, Alinovi R, Pasquale MF, Zacchello F, et al. Exhaled breath condensate cysteinyl leukotrienes are increased in children with exercise-induced bronchoconstriction. J Allergy Clin Immunol. 2005;115(4):764–70.

Choi IS, Ki WJ, Kim TO, Han ER, Seo IK. Seasonal factors influencing exercise-induced asthma. Allergy Asthma Immunol Res. 2012;4(4):192–8.

Chong LK, Suvarna K, Chess-Williams R, Peachell PT. Desensitization of b_2-adrenoceptor-mediated responses by short-acting b_2-adrenoceptor agonists in human lung mast cells. Br J Pharmacol. 2003;138:512–20.

Clee MD, Ingram CG, Reid PC, Robertson AS. The effect of astemizole on exercise-induced asthma. Br J Dis Chest. 1984;78(2):180–3.

Cockcroft D, Davis B. Direct and indirect challenges in the clinical assessment of asthma. Ann Allergy Asthma Immunol. 2009;103(5):363–9; quiz 9-72, 400.

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;6:523–6.

Coreno A, Skowronski M, Kotaur C, McFadden ER. Comparative effects of long-acting b_2-agonists, leukotriene antagonists, and a 5-lipoxygenase inhibitor on exercise-induced asthma. J Allergy Clin Immunol. 2000;106:500–6.

Couillard S, Bougault V, Turmel J, Boulet LP. Perception of bronchoconstriction following methacholine and eucapnic voluntary hyperpnea challenges in elite athletes. Chest. 2014;145(4):794–802.

Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing – 1999. Am J Respir Crit Care Med. 2000;161:309–29.

Dahlén B, Roquet A, Inman MD, Karlsson Ö, Naya I, Anstrén G, et al. Influence of zafirlukast and loratadine on exercise-induced bronchoconstriction. J Allergy Clin Immunol. 2002;109(5 Pt 1):789–93.

Davis MS, Daviskas E, Anderson SD, Kotaru C, Hejal RB, Finigan JH, et al. Airway surface fluid desiccation during isocapnic hyperpnea. J Appl Physiol. 2003a;94(6):2545–7.

Davis BE, Reid JK, Cockcroft DW. Formoterol thrice weekly does not result in the development of tolerance to bronchoprotection. Can Respir J. 2003b;10(1):23–6.

Daviskas E, Gonda I, Anderson SD. Local airway heat and water vapour losses. Respir Physiol. 1991;84:115–32.

de Aguiar KB, Anzolin M, Zhang L. Global prevalence of exercise-induced bronchoconstriction in childhood: a meta-analysis. Pediatr Pulmonol. 2018;53(4):412–25.

De Baets F, Bodart E, Dramaix-Wilmet M, Van Daele S, de Bildering G, Masset S, et al. Exercise-induced respiratory symptoms are poor predictors of bronchoconstriction. Pediatr Pulmonol. 2005;39(4):301–5.

de Benedictis FM, Tuteri G, Pazzelli P, Solinas LF, Niccoli A, Parente C. Combination drug therapy for the prevention of exercise-induced bronchoconstriction in children. Ann Allergy Asthma Immunol. 1998;80(4):352–6.

de Benedictis FM, del Giudice MM, Forenza N, Decimo F, de Benedictis D, Capristo A. Lack of tolerance to the protective effect of montelukast in exercise-induced bronchoconstriction in children. Eur Respir J. 2006;28(2):291–5.

de Menezes MB, Ferraz E, Brannan JD, Martinez EZ, Vianna EO. The efficacy and safety of mannitol challenge in a workplace setting for assessing asthma prevalence. J Asthma. 2018;1–8.

Dickinson J. Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods. Br J Sports Med. 2006;40(2):179–82.

Dougherty RH, Sidhu SS, Raman K, Solon M, Solberg OD, Caughey GH, et al. Accumulation of intraepithelial mast cells with a unique protease phenotype in T(H)2-high asthma. J Allergy Clin Immunol. 2010;125(5):1046–53.e8.

Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. Br Med Bull. 2000;56(4):1054–70.

Driessen JM, Nieland H, van der Palen JA, van Aalderen WM, Thio BJ, de Jongh FH. Effects of a single dose inhaled corticosteroid on the dynamics of airway obstruction after exercise. Pediatr Pulmonol. 2011;46(9):849–56.

Duffy P, Phillips YY. Caffeine consumption decreases the response to bronchoprovocation challenge with dry gas hyperventilation. Chest. 1991;99:1374–7.

Duong M, Subbarao P, Adelroth E, Obminski G, Strinich T, Inman M, et al. Sputum eosinophils and the response of exercise-induced bronchoconstriction to corticosteroid in asthma. Chest. 2008;133(2):404–11.

Duong M, Amin R, Baatjes AJ, Kritzinger F, Qi Y, Meghji Z, et al. The effect of montelukast, budesonide alone, and in combination on exercise-induced bronchoconstriction. J Allergy Clin Immunol. 2012;130(2):535–9.e3.

Edelman JM, Turpin JA, Bronsky EA. Oral Montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. Ann Intern Med. 2000;132:97–104.

Edmunds A, Tooley M, Godfrey S. The refractory period after exercise-induced asthma: its duration and relation to the severity of exercise. Am Rev Respir Dis. 1978;117:247–54.

Eggleston PA, Kagey-Sobotka A, Lichtenstein LM. A comparison of the osmotic activation of basophils and human lung mast cells. Am Rev Respir Dis. 1987;135:1043–8.

Eliasson AH, Phillips YY, Rajagopal KR, Howard RS. Sensitivity and specificity of bronchial provocation testing. An evaluation of four techniques in exercise-induced bronchospasm. Chest. 1992;102:347–55.

Elkins MR, Brannan JD. Warm-up exercise can reduce exercise-induced bronchoconstriction. Br J Sports Med. 2013;47(10):657–8.

Ellis EF. Inhibition of exercise-induced asthma by theophylline. J Allergy Clin Immunol. 1984;73(5 Pt 2):690–2.

Eschenbacher WL, Sheppard D. Respiratory heat loss is not the sole stimulus for bronchoconstriction induced by isocapnic hyperpnea with dry air. Am Rev Respir Dis. 1985;131:894–901.

Eveloff JL, Warnock DG. Activation of ion transport systems during cell volume regulation. Am J Physiol. 1987;252(Renal Electrolyte Phys 21):F1–F10.

Fahy JV, Wong HH, Geppetti P, Reis JM, Harris SC, Maclean DB, et al. Effect of an NK1 receptor antagonist (CP-99,994) on hypertonic saline-induced bronchoconstriction and cough in male asthmatic subjects. Am J Respir Crit Care Med. 1995;152:879–84.

Ferrari M, Balestreri F, Baratieri S, Biasin C, Oldani V, Lo Cascio V. Evidence of the rapid protective effect of formoterol dry-powder inhalation against exercise-

induced bronchospasm in athletes with asthma. Clin Invest. 2000;67:510–3.
Ferrari M, Segattini C, Zanon R, Bertaiola M, Balestreri F, Brotto E, et al. Comparison of the protective effect of salmeterol against exercise-induced bronchospasm when given immediately before a cycloergometric test. Respiration. 2002;69(6):509–12.
Finnerty JP, Holgate ST. Evidence for the roles of histamine and prostaglandins as mediators in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. Eur Respir J. 1990;3:540–7.
Finnerty JP, Wood-Baker R, Thomson H, Holgate S. Role of leukotrienes in exercise-induced asthma. Inhibitory effect of ICI 204219, a potent leukotriene D_4 receptor antagonist. Am Rev Respir Dis. 1992;145:746–9.
Fitch KD, Morton AR. Specificity of exercise in exercise-induced asthma. Br Med J. 1971;4:577–81.
Fitch KD, Sue-Chu M, Anderson SD, Boulet LP, Hancox RJ, McKenzie DC, et al. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22–24, 2008. J Allergy Clin Immunol. 2008;122(2):254–60, 260.e1–7
Frank PI, Morris JA, Hazell ML, Linehan MF, Frank TL. Long term prognosis in preschool children with wheeze: longitudinal postal questionnaire study 1993–2004. BMJ. 2008;336(7658):1423–6.
Freed AN, Davis MS. Hyperventilation with dry air increases airway surface fluid osmolality in canine peripheral airways. Am J Respir Crit Care Med. 1999;159(4):1101–7.
Freed AN, Omori C, Hubbard WC, Adkinson NF. Dry air- and hypertonic aerosol-induced bronchoconstriction and cellular responses in the canine lung periphery. Eur Respir J. 1994;7:1308–16.
Freed AN, Omori C, Schofield BH. The effect of bronchial blood flow on hyperpnea-induced airway obstruction and injury. J Clin Invest. 1995;96:1221–9.
Freed AN, McCulloch S, Meyers T, Suzuki R. Neurokinins modulate hyperventilation-induced bronchoconstriction in canine peripheral airways. Am J Respir Crit Care Med. 2003;167(8):1102–8.
Garcia R, Guerra P, Feo F, Galindo PA, Gomez E, Borja J, et al. Tachyphylaxis following regular use of formoterol in exercise-induced bronchospasm. J Investig Allergol Clin Immunol. 2001;11(3):176–82.
Gauvreau GM, Ronnen GM, Watson RM, O'Byrne PM. Exercise-induced bronchoconstriction does not cause eosinophilic airway inflammation or airway hyperresponsiveness in subjects with asthma. Am J Respir Crit Care Med. 2000;162:1302–7.
Ghosh SK, De Vos C, McIlroy I, Patel KR. Effect of cetirizine on exercise induced asthma. Thorax. 1991;46:242–4.
Global Initiative for Asthma. Global strategy for asthma and management and prevention. In: N. H. National Institutes of Health, Lung and Blood Institute, editors. NHLBI/WHO workshop report. Bethesda: Medical Communication Resources; Revised 2007a. p. 16–19. http://www.ginasthma.org
Global Initiative for Asthma. Global strategy for asthma and management and prevention. NHLBI/WHO workshop report. Bethesda: Medical Communication Resources; 2007b.
Godfrey S, Fitch KD. Exercise-induced bronchoconstriction: celebrating 50 years. Immunol Allergy Clin N Am. 2013;33(3):283–97, vii.
Godfrey S, Konig P. Exercise-induced bronchial lability in wheezy children and their families. Pediatrics. 1975a;56(5 pt-2 suppl):851–5.
Godfrey S, Konig P. Suppression of exercise-induced asthma by salbutamol, theophylline, atropine, cromolyn, and placebo in a group of asthmatic children. Pediatrics. 1975b;56:930–4.
Godfrey S, Konig P. Inhibition of exercise-induced asthma by different pharmacological pathways. Thorax. 1976;31(2):137–43.
Goldberg S, Schwartz S, Izbicki G, Hamami RB, Picard E. Sensitivity of exercise testing for asthma in adolescents is halved in the summer. Chest. 2005;128(4):2408–11.
Goldberg S, Mimouni F, Joseph L, Izbicki G, Picard E. Seasonal effect on exercise challenge tests for the diagnosis of exercise-induced bronchoconstriction. Allergy Asthma Proc. 2012;33(5):416–20.
Grzelewski T, Stelmach I. Exercise-induced bronchoconstriction in asthmatic children: a comparative systematic review of the available treatment options. Drugs. 2009;69(12):1533–53.
Gulliksson M, Palmberg L, Nilsson G, Ahlstedt S, Kumlin M. Release of prostaglandin D2 and leukotriene C in response to hyperosmolar stimulation of mast cells. Allergy. 2006;61(12):1473–9.
Hallstrand TS, Henderson WR Jr. An update on the role of leukotrienes in asthma. Curr Opin Allergy Clin Immunol. 2010;10(1):60–6.
Hallstrand TS, Curtis JR, Koepsell TD, Martin DP, Schoene RB, Sullivan SD, et al. Effectiveness of screening examinations to detect unrecognised exercise-induced bronchoconstriction. J Pediatr. 2002;141(3):343–9.
Hallstrand TS, Moody MW, Aitken ML, Henderson WR Jr. Airway immunopathology of asthma with exercise-induced bronchoconstriction. J Allergy Clin Immunol. 2005a;116(3):586–93.
Hallstrand TS, Moody MW, Wurfel MM, Schwartz LB, Henderson WR, Aitken ML. Inflammatory basis of exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2005b;172(6):679–86.
Hallstrand TS, Debley JS, Farin FM, Henderson WR Jr. Role of MUC5AC in the pathogenesis of exercise-induced bronchoconstriction. J Allergy Clin Immunol. 2007;119(5):1092–8.
Hallstrand TS, Lai Y, Henderson WR Jr, Altemeier WA, Gelb MH. Epithelial regulation of eicosanoid production in asthma. Pulm Pharmacol Ther. 2012;25(6):432–7.

Hancox RJ, Aldridge EE, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, et al. Tolerance to beta-agonists during acute bronchoconstriction. Eur Respir J. 1999;14(2):283–7.

Hancox RJ, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Taylor DR. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. Respir Med. 2000;94(8):767–71.

Hancox RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. Beta2-agonist tolerance and exercise-induced bronchospasm. Am J Respir Crit Care Med. 2002;165(8):1068–70.

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

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

Haney S, Hancox RJ. Overcoming beta-agonist tolerance: high dose salbutamol and ipratropium bromide. Two randomised controlled trials. Respir Res. 2007;8:19.

Hartley JPR, Charles TJ, Monie RDG, Seaton A, Taylor WH, Westood A, et al. Arterial plasma histamine after exercise in normal individuals and in patients with exercise induced asthma. Clin Sci. 1981;61:151–7.

Haverkamp HC, Dempsey JA, Miller JD, Romer LM, Pegelow DF, Lovering AT, et al. Repeat exercise normalizes the gas-exchange impairment induced by a previous exercise bout in asthmatic subjects. J Appl Physiol. 2005;99(5):1843–52.

Haverkamp HC, Dempsey JA, Pegelow DF, Miller JD, Romer LM, Santana M, et al. Treatment of airway inflammation improves exercise pulmonary gas exchange and performance in asthmatic subjects. J Allergy Clin Immunol. 2007;120(1):39–47.

Hayes MJ, Qing F, Rhodes CG, Rahman SU, Ind PW, Sriskandan S, et al. In vivo quantification of human pulmonary beta-adrenoceptors: effect of beta-agonist therapy. Am J Respir Crit Care Med. 1996;154(5): 1277–83.

Helenius I, Haahtela T. Allergy and asthma in elite summer sport athletes. J Allergy Clin Immunol. 2000;106(3): 444–52.

Helenius IJ, Tikkanen HO, Haahtela T. Association between type of training and risk of asthma in elite athletes. Thorax. 1997;52:157–60.

Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. Br J Sports Med. 1998;32:125–9.

Helenius I, Rytilä P, Sarna S, Lumme A, Helenius M, Remes V, et al. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. J Allergy Clin Immunol. 2002;109(6):962–8.

Hendrickson CD, Lynch JM, Gleeson K. Exercise induced asthma: a clinical perspective. Lung. 1994;172(1): 1–14.

Henriksen JM. Effect of inhalation of corticosteroids on exercise induced asthma: randomised double blind crossover study of budesonide in asthmatic children. Br Med J. 1985;291:248–9.

Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. Am Rev Respir Dis. 1984;130(6):1014–8.

Hofstra WB, Neijens HJ, Duiverman EJ, Kouwenberg JM, Mulder PG, Kuethe MC, et al. Dose-response over time to inhaled fluticasone propionate: treatment of exercise- and methacholine-induced bronchoconstriction in children with asthma. Pediatr Pulmonol. 2000;29(6): 415–23.

Holley AB, Cohee B, Walter RJ, Shah AA, King CS, Roop S. Eucapnic voluntary hyperventilation is superior to methacholine challenge testing for detecting airway hyperreactivity in nonathletes. J Asthma. 2012;49(6):614–9.

Holzer K, Anderson SD, Douglass J. Exercise in elite summer athletes: challenges for diagnosis. J Allergy Clin Immunol. 2002;110(3):374–80.

Holzer K, Anderson SD, Chan H-K, Douglass J. Mannitol as a challenge test to identify exercise-induced bronchoconstriction in elite athletes. Am J Respir Crit Care Med. 2003;167(4):534–47.

Hull JH, Hull PJ, Parsons JP, Dickinson JW, Ansley L. Approach to the diagnosis and management of suspected exercise-induced bronchoconstriction by primary care physicians. BMC Pulm Med. 2009;9:29.

Ichinose M, Miura M, Yamauchi H, Kageyama N, Tomaki M, Oyake T, et al. A neurokinin 1-receptor antagonist improves exercise-induced airway narrowing in asthmatic patients. Am J Respir Crit Care Med. 1996;153:936–41.

Iikura Y, Hashimoto K, Akasawa A, Katsunuma T, Ebisawa M, Saito H, et al. Serum theophylline concentration levels and preventative effects on exercise-induced asthma. Clin Exp Allergy. 1996;26(Suppl 2): 38–41.

Guidance for Industry. Development of drugs to prevent EIB. Draft guidance. US Dept of health and human services. 2002.

Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 1996;153:65–9.

Johnson M. Molecular mechanisms of b_2 adrenergic receptor function, response and regulation. J Allergy Clin Immunol. 2006;117:18–24.

Jonasson G, Carlsen KH, Blomqvist P. Clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma not previously treated with steroids. Eur Respir J. 1998;12:1099–104.

Jonasson G, Carlsen KH, Hultquist C. Low-dose budesonide improves exercise-induced bronchospasm

in schoolchildren. Pediatr Allergy Immunol. 2000;11(2):120–5.
Jones CO, Qureshi S, Rona RJ, Chinn S. Exercise-induced bronchoconstriction by ethnicity and presence of asthma in British nine year olds. Thorax. 1996;51(11):1134–6.
Kalra S, Swystun VA, Bhagat R, Cockcroft DW. Inhaled corticosteroids do not prevent the development of tolerance to the bronchoprotective effect of salmeterol. Chest. 1996;109:953–6.
Kang MJ, Lee SY, Kim HB, Yu J, Kim BJ, Choi WA, et al. Association of IL-13 polymorphisms with leukotriene receptor antagonist drug responsiveness in Korean children with exercise-induced bronchoconstriction. Pharmacogenet Genomics. 2008;18(7):551–8.
Karjalainen E-M, Laitinen A, Sue-Chu M, Altraja A, Bjermer L, Laitinen LA. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. Am J Respir Crit Care Med. 2000;161(6):2086–91.
Kelly KD, Spooner CH, Rowe BH. Nedocromil sodium *versus* sodium cromoglycate in treatment of exercise-induced bronchoconstriction: a systematic review. Eur Respir J. 2001;17:39–45.
Kemp JP, Dockhorn RJ, Busse WW, Bleecker ER. Prolonged effect of inhaled salmeterol against exercise-induced bronchospasm. Am J Respir Crit Care Med. 1994;150:1612–5.
Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. J Pediatr. 1998;133(3):424–8.
Kent SE, Bentley JH, Miller D, Sterling R, Menendez R, Tarpay M, et al. The effect of GSK2190915, a 5-lipoxygenase-activating protein inhibitor, on exercise-induced bronchoconstriction. Allergy Asthma Proc. 2014;35(2):126–33.
Kersten ET, van Leeuwen JC, Brand PL, Duiverman EJ, de Jongh FH, Thio BJ, et al. Effect of an intranasal corticosteroid on exercise induced bronchoconstriction in asthmatic children. Pediatr Pulmonol. 2012;47(1):27–35.
Kim JH, Lee SY, Kim HB, Jin HS, Yu JH, Kim BJ, et al. TBXA2R gene polymorphism and responsiveness to leukotriene receptor antagonist in children with asthma. Clin Exp Allergy. 2008;38(1):51–9.
Kippelen P, Anderson SD. Pathogenesis of exercise-induced bronchoconstriction. Immunol Allergy Clin N Am. 2013;33(3):299–312, vii.
Kippelen P, Larsson J, Anderson SD, Brannan JD, Dahlen B, Dahlen SE. Effect of sodium cromoglycate on mast cell mediators during hyperpnea in athletes. Med Sci Sports Exerc. 2010a;42(10):1853–60.
Kippelen P, Larsson J, Anderson SD, Brannan JD, Delin I, Dahlen B, et al. Acute effects of beclomethasone on hyperpnea-induced bronchoconstriction. Med Sci Sports Exerc. 2010b;42(2):273–80.
Kippelen P, Larsson J, Anderson SD. Acute effects of beclomethasone on hyperpnea-induced bronchoconstriction. Med Sci Sports Exerc. 2010c;42:273–80.
Kivity S, Ben Aharon Y, Man A, Topilsky M. The effect of caffeine on exercise-induced bronchoconstriction. Chest. 1990;97(5):1083–5.
Knopfli BH, Bar-Or O, Araujo CG. Effect of ipratropium bromide on EIB in children depends on vagal activity. Med Sci Sports Exerc. 2005;37(3):354–9.
Koh MS, Tee A, Lasserson TJ, Irving LB. Inhaled corticosteroids compared to placebo for prevention of exercise induced bronchoconstriction. Cochrane Database Syst Rev. 2007;18(3):CD002739.
Koskela HO, Lake C, Wong K, Brannan JD. Cough sensitivity to mannitol inhalation challenge identifies subjects with chronic cough. Eur Respir J. 2018;51.
Kukafka DS, Lang DM, Porter S, Rogers J, Ciccolella D, Polansky M, et al. Exercise-induced bronchospasm in high school athletes via a free running test: incidence and epidemiology. Chest. 1998;114(6):1613–22.
Kuzemko JA. Twenty years of sodium cromoglycate treatment: a short review. Respir Med. 1989;83:11–6.
Lai YL, Lee SP. Mediators in hyperpnea-induced bronchoconstriction of Guinea pigs. Naunyn Schmiedeberg's Arch Pharmacol. 1999;360(5):597–602.
Lai Y, Altemeier WA, Vandree J, Piliponsky AM, Johnson B, Appel CL, et al. Increased density of intraepithelial mast cells in patients with exercise-induced bronchoconstriction regulated through epithelially derived thymic stromal lymphopoietin and IL-33. J Allergy Clin Immunol. 2014;133(5):1448–55.
Larsson K, Ohlsén P, Malmberg P, Rydström P-O, Ulriksen H. High prevalence of asthma in cross country skiers. BMJ. 1993;307:1326–9.
Larsson J, Perry CP, Anderson SD, Brannan JD, Dahlen SE, Dahlen B. The occurrence of refractoriness and mast cell mediator release following mannitol-induced bronchoconstriction. J Appl Physiol (1985). 2011;110(4):1029–35.
Latimer KM, O'Byrne PM, Morris MM, Roberts R, Hargreave FE. Bronchoconstriction stimulated by airway cooling. Better protection with combined inhalation of terbutaline sulphate and cromolyn sodium than with either alone. Am Rev Respir Dis. 1983;128:440–3.
Lazarinis N, Jorgensen L, Ekstrom T, Bjermer L, Dahlen B, Pullerits T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. Thorax. 2014;69(2):130–6.
Lazo-Velasquez JC, Lozada AR, Cruz HM. Evaluation of severity of bronchial asthma through an exercise bronchial challenge. Pediatr Pulmonol. 2005;40(5):457–63.
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.
Lehnigk B, Rabe KF, Dent G, Herst RS, Carpentier PJ, Magnussen H. Effects of a 5-lipoxygenase inhibitor, ABT-761, on exercise-induced bronchoconstriction and urinary LTE_4 in asthmatic patients. Eur Respir J. 1998;11:617–23.
Lipworth BJ, Short PM, Williamson PA, Clearie KL, Fardon TC, Jackson CM. A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial. Chest. 2012;141(3):607–15.
Madhuban AA, Driessen JM, Brusse-Keizer MG, van Aalderen WM, de Jongh FH, Thio BJ. Association of the asthma control questionnaire with exercise-induced bronchoconstriction. J Asthma. 2011;48(3):275–8.
Magnussen H, Reuss G, Jörres R, Aurich R. The effect of azelasatine on exercise-induced asthma. Chest. 1988;93(5):937–40.
Magnussen H, Nowak D, Wiebicke W. Effect of inhaled ipratropium bromide on the airway response to methacholine, histamine, and exercise in patients with mild bronchial asthma. Respiration. 1992;59(1):42–7.
Malmberg LP, Pelkonen AS, Mattila PS, Hammaren-Malmi S, Makela MJ. Exhaled nitric oxide and exercise-induced bronchoconstriction in young wheezy children – interactions with atopy. Pediatr Allergy Immunol. 2009;20(7):673–8.
Manning PJ, Watson RM, Margolskee DJ, Williams VC, Schwartz JI, O'Byrne PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D4-receptor antagonist. N Engl J Med. 1990;323:1736–9.
Manning PJ, Watson RM, O'Byrne PM. Exercise-induced refractoriness in asthmatic subjects involves leukotriene and prostaglandin interdependent mechanisms. Am Rev Respir Dis. 1993;148:950–4.
Mannix ET, Farber MO, Palange P, Galassetti P, Manfredi F. Exercise-induced asthma in figure skaters. Chest. 1996;109:312–5.
Mannix ET, Manfredi F, Farber MO. A comparison of two challenge tests for identifying exercise-induced bronchospasm in figure skaters. Chest. 1999;115:649–53.
Mannix ET, Roberts M, Fagin DP, Reid B, Farber MO. The prevalence of airways hyperresponsiveness in members of an exercise training facility. J Asthma. 2003;40(4):349–55.
McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med. 2007;357(23):2348–58.
McFadden ER, Gilbert IA. Exercise-induced asthma. N Engl J Med. 1994;330:1362–7.
McFadden ER, Pichurko BM. Intraairway thermal profiles during exercise and hyperventilation in normal man. J Clin Invest. 1985;76:1007–10.
McFadden ER, Lenner KA, Strohl KP. Postexertional airway rewarming and thermally induced asthma. J Clin Invest. 1986;78:18–25.
McGraw DW, Liggett SB. Heterogeneity of beta adrenergic receptor kinase expression in the lung accounts for cell-specific desensitisation of the beta adrenergic receptor. J Biol Chem. 1997;272:7338–44.
McKenzie DC, McLuckie SL, Stirling DR. The protective effects of continuous and interval exercise in athletes with exercise-induced asthma. Med Sci Sports Exerc. 1994;26(8):951–6.
Melillo E, Woolley KL, Manning PJ, Watson RM, O'Byrne PM. Effect of inhaled PGE_2 on exercise-induced bronchoconstriction in asthmatic subjects. Am J Respir Crit Care Med. 1994;149:1138–41.
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.
Mickleborough TD, Gotshall RW, Kluka EM, Miller CW, Cordain L. Dietary chloride as a possible determinant of the severity of exercise-induced asthma. Eur J Appl Physiol. 2001;85(5):450–6.
Mickleborough TD, Murray RL, Ionescu AA, Lindley MR. Fish oil supplementation reduces severity of exercise-induced bronchoconstriction in elite athletes. Am J Respir Crit Care Med. 2003;168(10):1181–9.
Mickleborough TD, Lindley MR, Ray S. Dietary salt, airway inflammation, and diffusing capacity in exercise-induced asthma. Med Sci Sports Exerc. 2005;37(6):904–14.
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.
Mickleborough TD, Lindley MR, Turner LA. Comparative effects of a high-intensity interval warm-up and salbutamol on the bronchoconstrictor response to exercise in asthmatic athletes. Int J Sports Med. 2007;28(6):456–62.
Moloney ED, Griffin S, Burke CM, Poulter LW, O'Sullivan S. Release of inflammatory mediators from eosinophils following a hyperosmolar stimulus. Respir Med. 2003;97:1–5.
Molphy J, Dickinson J, Hu J, Chester N, Whyte G. Prevalence of bronchoconstriction induced by eucapnic voluntary hyperpnoea in recreationally active individuals. J Asthma. 2014;51(1):44–50.
Mountjoy M, Fitch K, Boulet LP, Bougault V, van Mechelen W, Verhagen E. Prevalence and characteristics of asthma in the aquatic disciplines. J Allergy Clin Immunol. 2015;136(3):588–94.
Munoz PA, Gomez FP, Manrique HA, Roca J, Barbera JA, Young IH, et al. Pulmonary gas exchange response to exercise- and mannitol- induced bronchoconstriction in mild asthma. J Appl Physiol. 2008;105(5):1477–85.
Naline E, Devillier P, Drapeau G, Toty L, Bakdach H, Regoli D, et al. Characterization of neurokinin effects and receptor selectivity in human isolated bronchi. Am Rev Respir Dis. 1989;140(3):679–86.

National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma – summary report 2007. J Allergy Clin Immunol. 2007;120:S94–138.

National Institutes of Health NH, Lung and Blood Institute. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-summary report 2007. Bethesda MD NHLBI/WHO workshop report Publication No 08–4051. J Allergy Clin Immonol. 2007;120(5 Suppl):S94–138.

Nelson JA, Strauss L, Skowronshi M, Ciufo R, Novak R, McFadden ER. Effect of long-term salmeterol treatment on exercise-induced asthma. N Engl J Med. 1998;339(3):141–6.

Newnham DM, Ingram CG, Earnshaw J, Palmer JBD, Dhillon DP. Salmeterol provides prolonged protection against exercise-induced bronchoconstriction in a majority of subjects with mild, stable asthma. Respir Med. 1993;87:439–44.

O'Byrne PM. Leukotrienes in the pathogenesis of asthma. Chest. 1997;111(Suppl 2):27S–34S.

O'Byrne PM. Leukotriene bronchoconstriction induced by allergen and exercise. Am J Respir Crit Care Med. 2000;161(2 Pt 2):S68–72.

O'Cain CF, Hensley MJ, McFadden ERJ, Ingram RH Jr. Pattern and mechanism of airway response to hypocapnia in normal subjects. J Appl Physiol Respir Environ Exerc Physiol. 1979;47(1):8–12.

O'Connor BJ, Aikman S, Barnes PJ. Tolerance to the non-bronchodilator effects of inhaled beta-agonists in asthma. N Engl J Med. 1992;327:1204–8.

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

O'Sullivan S, Roquet A, Dahlén B, Dahlén S-E, Kumlin M. Urinary excretion of inflammatory mediators during allergen-induced early and late phase asthmatic reactions. Clin Exp Allergy. 1998b;228:1332–9.

Park HK, Jung JW, Cho SH, Min KU, Kang HR. What makes a difference in exercise-induced bronchoconstriction: an 8 year retrospective analysis. PLoS One. 2014;9(1):e87155.

Parsons JP, Mastronarde JG. Exercise-induced bronchoconstriction in athletes. Chest. 2005;128(6): 3966–74.

Parsons JP, Kaeding C, Phillips GD, Jarjoura D, Wadley G, Mastronade JG. Prevalence of exercise-induced bronchospasm in a cohort of varsity college athletes. Med Sci Sports Exerc. 2007;39(9):1487–92.

Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2013;187(9):1016–27.

Passalacqua G, Canonica GW, Bousquet J. Structure and classification of H1-antihistamines and overview of their activities. Clin Allergy Immunol. 2002;17: 65–100.

Patel KR. Terfenadine in exercise-induced asthma. Br Med J. 1984;85:1496–7.

Patel KR, Wall RT. Dose-duration effect of sodium cromoglycate aerosol in exercise-induced asthma. Eur J Respir Dis. 1986;69:256–60.

Patel KR, Tullett WM, Neale MG, Wall RT, Tan KM. Plasma concentrations of sodium cromoglycate given by nebulisation and metered dose inhalers in patients with exercise-induced asthma: relationship to protective effect. Br J Clin Pharmacol. 1986;21(2):231–3.

Peachell P. Regulation of mast cells by b_2-agonists. Clin Rev Allergy Immunol. 2006;31(2–3):131–42.

Pearlman DS, Ostrom NK, Bronsky EA, Bonuccelli CM, Hanby LA. The leukotriene D_4-receptor antagonist zafirlukast attenuates exercise-induced bronchoconstriction in children. J Pediatr. 1999;134(3):273–9.

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

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

Pedersen S, Hansen OR. Budesonide treatment of moderate and severe asthma in children: a dose-response study. J Allergy Clin Immunol. 1995;95(1 Pt 1):29–33.

Pedersen L, Winther S, Backer V, Anderson SD, Larsen KR. Airway responses to eucapnic hyperpnea, exercise and methacholine in elite swimmers. Med Sci Sports Exerc. 2008;40(9):1567–72.

Peroni DG, Piacentini GL, Ress M, Bodini A, Loiacono A, Aralla R, et al. Time efficacy of a single dose of montelukast on exercise-induced asthma in children. Pediatr Allergy Immunol. 2002a;13(6):434–7.

Peroni DG, Piacentini GL, Pietrobelli A, Loiacono A, De Gasperi W, Sabbion A, et al. The combination of single-dose montelukast and loratadine on exercise-induced bronchospasm in children. Eur Respir J. 2002b;20(1):104–7.

Philip G, Villaran C, Pearlman DS, Loeys T, Dass SB, Reiss TF. Protection against exercise-induced bronchoconstriction two hours after a single oral dose of montelukast. J Asthma. 2007a;44(3):213–7.

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

Phillips YY, Jaeger JJ, Laube BL, Rosenthal RR. Eucapnic voluntary hyperventilation of compressed gas mixture. A simple system for bronchial challenge by respiratory heat loss. Am Rev Respir Dis. 1985;131:31–5.

Pohjantahti H, Laitinen J, Parkkari J. Exercise-induced bronchospasm among healthy elite cross country skiers and non-athletic students. Scand J Med Sci Sports. 2005;15(5):324–8.

Poppius H, Sovijarvi ARA, Tammilehto L. Lack of protective effect of high-dose ipratropium on

bronchoconstriction following exercise with cold air breathing in patients with mild asthma. Eur J Respir Dis. 1986;68:319–25.

Porsbjerg C, Brannan JD, Anderson SD, Backer V. Relationship between airway responsiveness to mannitol and to methacholine and markers of airway inflammation, peak flow variability and quality of life in asthma patients. Clin Exp Allergy. 2008;38(1):43–50.

Price OJ, Ansley L, Hull JH. Diagnosing exercise-induced bronchoconstriction with eucapnic voluntary hyperpnea: is one test enough? J Allergy Clin Immunol Pract. 2015;3(2):243–9.

Price OJ, Ansley L, Levai IK, Molphy J, Cullinan P, Dickinson JW, et al. Eucapnic voluntary hyperpnea testing in asymptomatic athletes. Am J Respir Crit Care Med. 2016;193(10):1178–80.

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.

Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. Respir Med. 1994;88:363–8.

Randolph C. Pediatric exercise-induced bronchoconstriction: contemporary developments in epidemiology, pathogenesis, presentation, diagnosis, and therapy. Curr Allergy Asthma Rep. 2013;13(6):662–71.

Randolph CC, Dreyfus D, Rundell KW, Bangladore D, Fraser B. Prevalence of allergy and asthma symptoms in recreational roadrunners. Med Sci Sports Exerc. 2006;38(12):2053–7.

Reiss TF, Hill JB, Harman E, Zhang J, Tanaka WK, Bronsky E, et al. Increased urinary excretion of LTE_4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. Thorax. 1997;52(12):1030–5.

Rossing TH, Weiss JW, Breslin FJ, Ingram RH Jr, McFadden ERJ. Effects of inhaled sympathomimetics on obstructive response to respiratory heat loss. J Appl Physiol. 1982;52(5):1119–23.

Rouhos A, Ekroos H, Karjalainen J, Sarna S, Sovijarvi AR. Exhaled nitric oxide and exercise-induced bronchoconstriction in young male conscripts: association only in atopics. Allergy. 2005;60(12):1493–8.

Rundell KW. High levels of airborne ultrafine and fine particulate matter in indoor ice arenas. Inhal Toxicol. 2003;15(3):237–50.

Rundell KW, Caviston R. Ultrafine and fine particulate matter inhalation decreases exercise performance in healthy subjects. J Strength Cond Res. 2008;22(1):2–5.

Rundell KW, Slee JB. Exercise and other indirect challenges to demonstrate asthma or exercise-induced bronchoconstriction in athletes. J Allergy Clin Immunol. 2008;122(2):238–46; quiz 47–8.

Rundell KW, Wilber RL, Szmedra L, Jenkinson DM, Mayers LB, Im J. Exercise-induced asthma screening of elite athletes: field vs laboratory exercise challenge. Med Sci Sports Exerc. 2000;32(2):309–16.

Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. Med Sci Sports Exerc. 2001;33(2):208–13.

Rundell KW, Spiering BA, Judelson DA, Wilson MH. Bronchoconstriction during cross-country skiing: is there really a refractory period? Med Sci Sports Exerc. 2003;35(1):18–26.

Rundell KW, Spiering BA, Evans TM, Baumann JM. Baseline lung function, exercise-induced bronchoconstriction, and asthma-like symptoms in elite women ice hockey players. Med Sci Sports Exerc. 2004a;36(3):405–10.

Rundell KW, Anderson SD, Spiering BA, Judelson DA. Field exercise vs laboratory eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes. Chest. 2004b;125:909–15.

Rundell K, Spiering BA, Baumann JM, Evans TM. Effects of montelukast on airway narrowing from eucapnic voluntary hyperventilation and cold air exercise. Br J Sports Med. 2005;39(4):232–6.

Rundell KW, Caviston R, Hollenbach AM, Murphy K. Vehicular air pollution, playgrounds, and youth athletic fields. Inhal Toxicol. 2006;18(8):541–7.

Rundell KW, Hoffman JR, Caviston R, Bulbulian R, Hollenbach AM. Inhalation of ultrafine and fine particulate matter disrupts systemic vascular function. Inhal Toxicol. 2007;19(2):133–40.

Rundell KW, Anderson SD, Sue-Chu M, Bougault V, Boulet LP. Air quality and temperature effects on exercise-induced bronchoconstriction. Compr Physiol. 2015;5(2):579–610.

Sallaoui R, Chamari K, Mossa A, Tabka Z, Chtara M, Feki Y, et al. Exercise-induced bronchoconstriction and atopy in Tunisian athletes. BMC Pulm Med. 2009;9:8.

Sano F, Sole D, Naspitz CK. Prevalence and characteristics of exercise-induced asthma in children. Pediatr Allergy Immunol. 1998;9(4):181–5.

Schoeffel RE, Anderson SD, Gillam I, Lindsay DA. Multiple exercise and histamine challenge in asthmatic patients. Thorax. 1980;35:164–70.

Schoeffel RE, Anderson SD, Lindsay DA. Sodium Cromoglycate as a pressurized aerosol (Vicrom) in exercise-induced asthma. Aust NZ J Med. 1983;13:157–61.

Scola AM, Chong LK, Suvarna SK, Chess-Williams R, Peachell PT. Desensitisation of mast cell b_2-adrenoceptor-mediated responses by salmeterol and formoterol. Br J Pharmacol. 2004;141(1):163–71.

Scollo M, Zanconato S, Ongaro R, Zaramella C, Zacchello F, Baraldi E. Exhaled nitric oxide and exercise-induced bronchoconstriction in asthmatic children. Am J Respir Crit Care Med. 2000;161:1047–50.

Seale JP, Anderson SD, Lindsay DA. A comparison of oral theophylline and oral salbutamol in exercise-induced asthma. Aust NZ J Med. 1977;7:270–4.

Seccombe LM, Buddle L, Brannan JD, Peters MJ, Farah CS. Exercise-induced bronchoconstriction with

firefighting contained breathing apparatus. Med Sci Sports Exerc. 2018;50(2):327–33.
Shturman-Ellstein R, Zeballos RJ, Buckley JM, Souhrada JF. The beneficial effect of nasal breathing on exercise-induced bronchoconstriction. Am Rev Respir Dis. 1978;118:65–73.
Silverman M, Andrea T. Time course of effect of disodium cromoglycate on exercise-induced asthma. Arch Dis Child. 1972;47(253):419–22.
Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. Pediatrics. 1997;99(5): 655–9.
Simpson AJ, Tufvesson E, Anderson SD, Romer LM, Bjermer L, Kippelen P. Effect of terbutaline on hyperpnoea-induced bronchoconstriction and urinary club cell protein 16 in athletes. J Appl Physiol (1985). 2013;115(10):1450–6.
Simpson AJ, Romer LM, Kippelen P. Self-reported symptoms after induced and inhibited bronchoconstriction in athletes. Med Sci Sports Exerc. 2015;47:2005–13.
Simpson AJ, Bood JR, Anderson SD, Romer LM, Dahlen B, Dahlen SE, et al. A standard, single dose of inhaled terbutaline attenuates hyperpnea-induced bronchoconstriction and mast cell activation in athletes. J Appl Physiol (1985). 2016;120(9):1011–7.
Spooner C, Spooner G, Rowe B. Mast-cell stabilising agents to prevent exercise-induced bronchoconstriction. Cochrane Database Syst Rev. 2003;4:CD002307.
SMTEC. EucapSYS system for eucapnic voluntary hyperpnea. 2014.
Stadelmann K, Stensrud T, Carlsen KH. Respiratory symptoms and bronchial responsiveness in competitive swimmers. Med Sci Sports Exerc. 2011;43(3):375–81.
Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. J Allergy Clin Immunol. 2008;121(2):383–9.
Stensrud T, Mykland KV, Gabrielsen K, Carlsen KH. Bronchial hyperresponsiveness in skiers: field test versus methacholine provocation? Med Sci Sports Exerc. 2007;39(10):1681–6.
Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyperresponsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet. 2008;372(9643): 1058–64.
Stickland MK, Rowe BH, Spooner CH, Vandermeer B, Dryden DM. Effect of warm-up exercise on exercise-induced bronchoconstriction. Med Sci Sports Exerc. 2012;44(3):383–91.
Storms W, Chervinsky P, Ghannam AF, Bird S, Hustad CM, Edelman JM. A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. Respir Med. 2004;98(11):1051–62.
Subbarao P, Duong M, Adelroth E, Otis J, Obminski G, Inman M, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. J Allergy Clin Immunol. 2006;117(5):1008–13.
Sue-Chu M, Larsson L, Moen T, Rennard SI, Bjermer L. Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without "ski asthma". Eur Respir J. 1999a;13(3):626–32.
Sue-Chu M, Henriksen AH, Bjermer L. Non-invasive evaluation of lower airway inflammation in hyperresponsive elite cross-country skiers and asthmatics. Respir Med. 1999b;93(10):719–25.
Sue-Chu M, Brannan JD, Anderson SD, Chew N, Bjermer L. Airway responsiveness to methacholine (Mch), adenosine 5-monophosphate (AMP), mannitol (Man), eucapnic voluntary hyperpnea (EVH) and sport specific field exercise challenge (Ex) in cross country ski athletes. Eur Respir J. 2002;20(Suppl 38):410s.
Sue-Chu M, Brannan JD, Anderson SD, Chew N, Bjermer L. Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers. Br J Sports Med. 2010;44(11):827–32.
Swystun VA, Gordon JR, Davis EB, Zhand X, Cockcroft DW. Mast cell tryptase release and asthmatic responses to allergen increase with regular use of salbutamol. J Allergy Clin Immunol. 2000;106:57–64.
Tabka Z, Ben Jebria A, Vergeret J, Guenard H. Effect of dry warm air on respiratory water loss in children with exercise-induced asthma. Chest. 1988;94:81–6.
Tahan F, Saraymen R, Gumus H. The role of lipoxin A4 in exercise-induced bronchoconstriction in asthma. J Asthma. 2008;45(2):161–4.
Tan RA, Spector SL. Exercise-induced asthma: diagnosis and management. Ann Allergy. 2002;89:226–36.
Taylor-Clark TE, Nassenstein C, Undem BJ. Leukotriene D4 increases the excitability of capsaicin-sensitive nasal sensory nerves to electrical and chemical stimuli. Br J Pharmacol. 2008;154(6):1359–68.
Tecklenburg SL, Mickleborough TD, Fly AD, Bai Y, Stager JM. Ascorbic acid supplementation attenuates exercise-induced bronchoconstriction in patients with asthma. Respir Med. 2007;101(8):1770–8.
Thio BJ, Slingerland GLM, Nagelkerke AF, Roord JJ, Mulder PGH, Dankert-Roelse JE. Effects of single-dose fluticasone on exercise-induced asthma in asthmatic children: a pilot study. Pediatr Pulmonol. 2001;32:115–21.
Tilles SA. Vocal cord dysfunction in children and adolescents. Curr Allergy Asthma Rep. 2003;3(6):467–72.
Timmer W, Lecher V, Birraux G, Neuhäuser M, Hatzelmann A, Bethke T, et al. The phosphodiesterase 4 inhibitor roflumilast is efficacious in exercise-induced asthma and leads to suppression of LPS-stimulated TNF-a ex vivo. J Clin Pharmacol. 2002;42:297–303.
Tullett WM, Tan KM, Wall RT, Patel KR. Dose-response effect of sodium cromoglycate pressurised aerosol in exercise induced asthma. Thorax. 1985;40:41–4.

Ucok K, Dane S, Gokbel H, Akar S. Prevalence of exercise-induced bronchospasm in long distance runners trained in cold weather. Lung. 2004;182(5):265–70.

van Leeuwen JC, Driessen JM, Kersten ET, Thio BJ. Assessment of exercise-induced bronchoconstriction in adolescents and young children. Immunol Allergy Clin N Am. 2013;33(3):381–94, viii–ix.

van Schoor J, Joos GF, Kips JC, Drajesk JF, Carpentier PJ, Pauwels RA. The effect of ABT-761, a novel 5-lipoxygenase inhibitor, on exercise- and adenosine-induced bronchoconstriction in asthmatic subjects. Am J Respir Crit Care Med. 1997;155:875–80.

van Veen WJ, Driessen JMM, Kersten ETG, van Leeuwen JC, Brusse-Keizer MGJ, van Aalderen WMC, et al. BMI predicts exercise induced bronchoconstriction in asthmatic boys. Pediatr Pulmonol. 2017;52(9):1130–4.

VanHaitsma TA, Mickleborough T, Stager JM, Koceja DM, Lindley MR, Chapman R. Comparative effects of caffeine and albuterol on the bronchoconstrictor response to exercise in asthmatic athletes. Int J Sports Med. 2010;31(4):231–6.

Vidal C, Fernández-Ovide E, Piñeiro J, Nuñez R, González-Quintela A. Budesonide or montelukast prevents exercise-induced bronchoconstriction. Ann Allergy Asthma Immunol. 2001;86:655–8.

Villaran C, O'Neill J, Helbling A, van Noord JA, Lee TH, Chuchalin AG, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. J Allergy Clin Immunol. 1999;104(3 Part 1):547–53.

Vilsvik J, Ankerst J, Palmqvist M, Persson G, Schaanning J, Schwabe G, et al. Protection against cold air and exercise-induced bronchoconstriction while on regular treatment with Oxis®. Respir Med. 2001;95:484–90.

Visser R, Wind M, de Graaf B, de Jongh FH, van der Palen J, Thio BJ. Protective effect of a low single dose inhaled steroid against exercise induced bronchoconstriction. Pediatr Pulmonol. 2014.

Voutilainen M, Malmberg LP, Vasankari T, Haahtela T. Exhaled nitric oxide indicates poorly athlete's asthma. Clin Respir J. 2013;7(4):347–53.

Wasfi YS, Kemp JP, Villaran C, Massaad R, Xin W, Smugar SS, et al. Onset and duration of attenuation of exercise-induced bronchoconstriction in children by single-dose of montelukast. Allergy Asthma Proc. 2011;32(6):453–9.

Weiler JM, Ryan EJ 3rd. Asthma in United States olympic athletes who participated in the 1998 Olympic winter games. J Allergy Clin Immunol. 2000;106(2):267–71.

Weiler JM, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Games. J Allergy Clin Immunol. 1998;102(5):722–6.

Weiler JM, Nathan RA, Rupp NT, Kalberg CJ, Emmett A, Dorinsky PM. Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. Ann Allergy Asthma Immunol. 2005;94:65–72.

Weiler JM, Bonini S, Coifman R, Craig T, Delgado L, Capao-Filipe M, et al. American academy of allergy, asthma & immunology work group report: exercise-induced asthma. J Allergy Clin Immunol. 2007;119(6):1349–58.

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.e36.

Weinberger M, Abu-Hasan M. Perceptions and pathophysiology of dyspnea and exercise intolerance. Pediatr Clin N Am. 2009;56(1):33–48, ix.

Wiebicke W, Poynter A, Montgomery M, Chernick V, Pasterkamp H. Effect of terfenadine on the response to exercise and cold air in asthma. Pediatr Pulmonol. 1988;4:225–9.

Wilber RL, Rundell L, Szmedra L, Jenkinson DM, Im J, Drake SD. Incidence of exercise-induced bronchospasm in Olympic Winter Sport athletes. Med Sci Sports Exerc. 2000;32(4):732–7.

Williams NC, Johnson MA, Hunter KA, Sharpe GR. Reproducibility of the bronchoconstrictive response to eucapnic voluntary hyperpnoea. Respir Med. 2015;109(10):1262–7.

Wilson BA, Bar-Or O, O'Byrne PM. The effects of indomethacin on refractoriness following exercise both with and without bronchoconstriction. Eur Respir J. 1994;12:2174–8.

Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, et al. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. Proc Natl Acad Sci U S A. 2007;104(40):15858–63.

Woolley M, Anderson SD, Quigley B. Duration of protective effect of terbutaline sulphate and cromolyn sodium alone and in combination on exercise-induced asthma. Chest. 1990;97:39–45.

Wraight JM, Hancox RJ, Herbison GP, Cowan JO, Flannery EM, Taylor DR. Bronchodilator tolerance: the impact of increasing bronchoconstriction. Eur Respir J. 2003;21(5):810–5.

Yates DH, Kharitonov S, Barnes PJ. An inhaled glucocorticoid does not prevent tolerance to the protective effect of a long-acting inhaled beta 2-agonist. Am J Respir Crit Care Med. 1996;154:1603–7.

Zielinski J, Chodosowska E. Exercise-induced bronchoconstriction in patients with bronchial asthma. Its prevention with an antihistaminic agent. Respiration. 1977;34(1):31–5.