The Role of Physical Exercise and the Treatment of Allergic Rhinitis in Childhood Asthma

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VRIJE UNIVERSITEIT

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1

General introduction

1.1 Asthma in childhood

Asthma is a chronic inflammatory disease of the bronchial mucosa leading to reversible airflow obstruction, either spontaneously or with treatment. The lower airways show hyperresponsiveness to a variety of stimuli leading to mild to severe airway obstruction. The prevalence of asthma has increased over the past 20 years in industrialised countries, with the largest increase in persons under 18 years of age[1]. In The Netherlands the symptom-based prevalence of asthma in childhood (6-13 years) is 11%[2]. Only half of these children were diagnosed by a physician, indicating that asthma in childhood is still underdiagnosed[2]. Suspected reasons for the increase in asthma prevalence include an increase in maternal smoking and exposure to indoor allergens, such as house dust mite and pets [3].

A detailed medical history may suggest that a patient suffers from asthma. The main symptoms of asthma are intermittent episodes of dyspnoea, wheezing, chest tightness and cough. An important feature of asthma is the variability of the airway narrowing over time. Diagnosis may be difficult, especially in infancy when transient wheezing due to a small airway calibre may mimic asthma[4]. Recently, for epidemiological purposes bronchial hyperresponsiveness, as measured with a lung function test with the presence of wheezing in the previous 12 months, has been used to define asthma[3]. However, bronchial hyperresponsiveness is not a specific feature of asthma[5].

The treatment of asthma has evolved over the years, from efforts merely to improve symptoms to prevention of symptoms i.e. the movement from drugs that interact with the smooth muscle and nerves (e.g. beta-agonists and cholinergics) to drugs that prevent and suppress airway inflammation and oedema (corticosteroids and leucotriene-modulating drugs). Another shift in the treatment has been from systemic towards topical treatment. The benefits of topical drug administration include a low risk of systemic adverse effects, rapid onset of action and good therapeutic effect.

1.2 Pathophysiology of asthma and allergic rhinitis: the allergic reaction

The upper and lower airways are lined by the same pseudo-stratified ciliated columnar epithelium, with goblet cells and seromucous glands. All areas of the respiratory tract are exposed to the same inhaled antigens and irritants and display the same immunopathological responses to challenges. Both allergic rhinitis and asthma are characterised by mucosal inflammation and an immunologic response modulated by IgE. The initial presence of antigens in the mucosa prompts the formation of IgE antibodies, which bind to high affinity receptors in the cell membrane of the mast cells and basophils in the respiratory epithelium. At a subsequent exposure to the antigen an antigen-antibody complex is formed at the mast cell or basophil when an allergen connects with two cellbound IgE molecules. This leads to the release of several preformed mediators and de novo synthesised mediators in the so-called early phase, that is mast cell mediated (Figure 1)[6]. Released preformed mediators are histamine, tryptase, neutral proteases, heparin, chymase and acid hydrolases.

Newly generated mediators include adenosine, prostaglandin D_2, leucotriene C_4, cytokines and kinins[7]. All mediators except histamine are formed from arachidonic acid, a prominent phospholipid related to the cell membrane. The released mediators interact with neural elements, mucosal glands, and blood vessels causing immediate symptoms as well as chemotaxis of inflammatory cells. Histamine is an important mediator of the allergic response in the early phase in the respiratory mucosa. Its release stimulates sensory nerves, causing pruritus of the nose, palate, and conjunctiva. The resultant excitation of parasympatic reflexes contributes to vasodilatation and mucus hypersecretion[6]. Kinins stimulate afferent neurones inducing vasodilatation and oedema.

In about 50% of patients an additional late phase reaction occurs (4-24 hour after challenge). Mucosal biopsies taken at that time show increased numbers of eosinophils, basophils, neutrophils and T- lymphocytes that are attracted as a result of chemotaxis. Cytotoxic proteins released by activated eosinophils cause damage to epithelial cells. The late phase is characterised by a preferential expression of a T helper type 2 (Th2) cytokine profile [predominantly interleukin-4 (IL-4) and interleukin-5 (IL-5)] 8. This pattern of cytokine expression is recognised as a pivotal event in the development of the late phase response. Th2 type cytokines are implicated in the local IgE production, in the mast cell /basophil allergen responsiveness and maturation, and in the recruitment, activation and survival of eosinophils. IL-4 increases expression of vascular cell adhesion molecules (VCAM) in endothelial cells facilitating the migration of inflammatory cells into tissue sites. VCAM induces uncommitted T cells towards the Th_2 phenotype, in this way perpetuating the allergic reaction. In the late phase, rechallenged subjects are hypersensitive to the allergen and will display increased mediator release and symptoms.

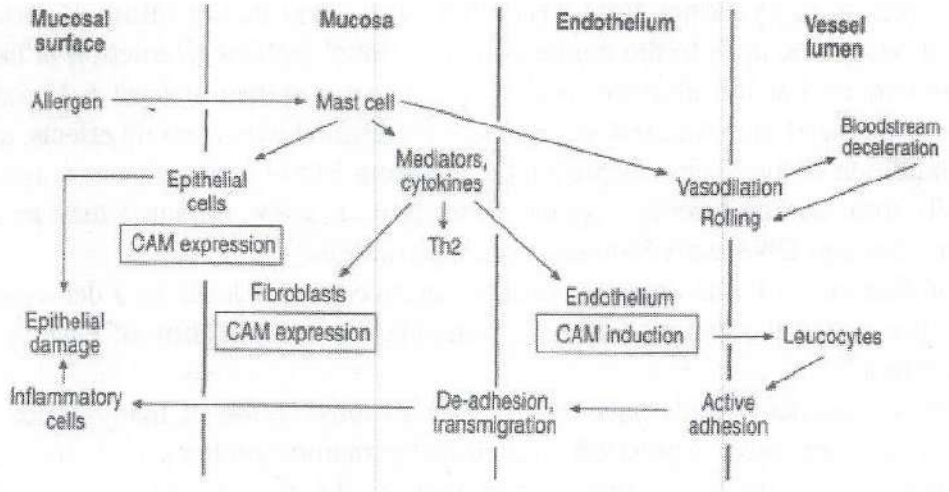

Figure 1: The pathophysiology of allergic disorders. Reprinted with permission from Eur Respir Rev 1997; 7:47, 286-28. Munksgaard International Publishers Ltd. Copenhagen, Denmark.

Repeated exposure to an allergen increases the sensitivity to the specific allergen but also to non-specific stimuli such as cold air, and cigarette smoke (in allergic rhinitis

this phenomenon is called 'priming'[9]). The possible explanation for this hypersensitive state is that the inflamed mucosa is permitting more antigen to penetrate into the mucosa. (Buckle et al demonstrated more penetration of topically applied radiolabeled albumin in the mucosa of allergic rhinitis patients compared to healthy persons[10]). Other factors may be the increased sensitivity of sensory nerve endings, the increased number of receptors and the sensitivity of resident cells.

1.3 Topical corticosteroids in asthma and allergic rhinitis

1.3.1 Pharmacology

The primary action of corticosteroids in asthma and allergic rhinitis is the diminution of the effects of the allergic reaction. The efficacy of nasal corticosteroids is attained mostly by a local effect[11,12]. Glucocorticoid molecules diffuse passively through the cell membrane, enter the cytoplasm and bind to the corticosteroid receptor[13]. On binding the corticosteroid receptor complex moves into the nucleus, where it attaches to specific binding sites in the DNA[14]. An increase in mRNA chain synthesis follows leading to the formation of lipocortin, neutral endopeptidases and inhibitors of plasminogen activator. Lipocortin inhibits the synthesis and release of arachidonic-derived mediators of inflammation, such as prostaglandins, thromboxanes and leukotrienes, from phospholipids by its inhibitory action on phospholipase A_2. Steroids also suppress the transcription of genes coding for the production of inflammatory proteins. The inhibitory activity of corticosteroids on prostaglandin synthesis is probably at least partially responsible for the vasoconstrictive and anti-oedematous effect of corticosteroid[15]. This vasoconstrictive effect of corticosteroids can also be caused by their stimulatory action on the β-adrenergic receptor. Corticosteroids also decrease the response of mucosal glands to cholinergic stimulation[16], decrease release of cytokines from TH_2 lymfocytes[17] and inhibit influx of eosinophils and basophilic cells to the epithelium. The initial cellular interaction is likely to be immediate but the ultimate clinical expression requires at least 6-12 hours because of the need to induce and secrete new proteins. However some effects, such as the inhibition of the release of prostaglandins from endothelial cells or the release of ACTH from certain tumours, appear faster (within a few minutes) than can be explained through DNA activation and protein synthesis [17,18].

The modification of the allergic response by corticosteroids leads to a decrease of chemo-attraction and adherence of cells, reducing the accumulation of eosinophils and basophils [19,20].

In conclusion corticosteroids have effects on the transcription of many genes, resulting in an increased expression of anti-inflammatory proteins and decreased expression of inflammatory proteins. This reduces the recruitment of T lymphocytes, eosinophils and mast cells and, thereby decreasing mucosal inflammation. The mode of action of the fast anti-inflammatory effects of corticosteroids is unclear.

1.3.2 Pharmacokinetics

The advantage of topical administration of drugs on the airway mucosa is that a high concentration of drug can be delivered on the target organ. A major drawback is the inability to reach all mucous membranes with topical application. Any drug deposited on the respiratory mucosa should be hydrophilic to dissolve in the mucous layer as well as lipophilic to be absorbed through cell membranes. The total process must be completed before the drug is removed by mucociliary clearance. The majority of the drug, whether intranasally deposited or inhaled is transported towards the nasopharynx, from where it is swallowed[21]. Systemic absorption after swallowing is dependent on absorption in the gut and first-pass metabolism of the drug in the liver. Systemic bio-availability of an intranasal or an orally inhaled drug is the sum of the amount of the drug absorbed from the respiratory mucosa plus the part absorbed from the gut after swallowing, not metabolised by the liver (oral bioavailability).

Fluticasone, budesonide and beclomethasone are potent steroids that are used for both intranasal and pulmonary application. Both fluticasone and budesonide have a low oral bioavailability; their systemic bioavailability is mainly determined by the absorption from the airway mucosa. The oral bioavailability of beclomethason is higher compared to fluticasone and budesonide[22,23]. Fluticasone and beclomethason have a long elimination half-life (8-14 hrs.) compared to Budesonide[24]. Drugs that have a half-life of the same magnitude or longer as the dosing interval tend to accumulate. The effect of differences in half-life on side effects is not known. Studies with oral prednisone, comparing the effect of daily with alternate day dosing on the hypothalamic-pituitary-adrenal axis, suggest that the effect is more dependent on persistent plasma levels than on peak plasma concentrations[25].

1.4 Aims of the study

This thesis deals with some of the conditions influencing clinical asthma. First the influence of allergic rhinitis on the severity of asthma was studied and whether this influence can be modified by the use of intranasal corticosteroids. To that end we raised the following questions:

1. Can intranasal steroids decrease asthmatic symptoms in patients with allergic rhinitis and asthma? In Chapter 3 a systematic review of the literature on this subject is presented.
2. Is the increase in bronchial responsiveness in patients with asthma and allergic rhinitis during natural allergic exposure preventable by the use of intranasal corticosteroids? To test this hypothesis we studied the effect of intranasal fluticasone on the bronchial responsiveness to metacholine in children and young adults with allergic rhinitis and asthma during the grass pollen season. In the consecutive pollen season we compared the effect of intranasal fluticasone with beclomethason on the evolution of bronchial responsiveness to metacholine in children and young adults with allergic rhinitis and asthma (Chapter 4).

Secondly the following questions were studied:

1. What is the role of the mucosa, both in the upper and lower airway, in the pathophysiologic mechanisms leading to exercise-induced bronchial obstruction (EIB)? A review of the literature of the pathophysiology of EIB is presented and its implications for therapy in Chapter 5.
2. Normalising cardiovascular fitness has been suggested to be beneficial in reducing the severity of EIB, although there is no evidence for this hypothesis. Therefore we studied if a relationship can be found between cardiovascular fitness and the severity of EIB (Chapter 6).
3. Effective pre-exercise prophylaxis has been considered to be a pre-requisite when children with EIB undertake a training programme aimed at increasing cardiovascular fitness. Is a physical training programme feasible in children with EIB if prophylaxis against EIB consists of a warm-up and a cool-down instead of pre-exercise bronchodilators? (Chapter 7)
4. A single high dose of inhaled steroid increases upper airway calibre in children with laryngitis subglottica and is effective in childhood asthma attacks. It has been suggested that vasoconstrictive and anti-edematous activity accounts for the rapid beneficial effect of a single high dose of inhaled steroid. We hypothesised that if increased vascularity plays a role in the pathophysiology of EIB, a single high dose of inhaled steroid may have an acute protective effect against EIB. Can a single high dose of topical corticosteroid reduce the degree of EIB? (Chapter 8)

1.5 References

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2

The association between allergic rhinitis and asthma

2.1 Epidemiology of allergic rhinitis in association with asthma

Allergic rhinitis is the most common chronic allergic disease in industrialised countries with a prevalence varying from 5 to 40%[1,2] in different countries[3]. The prevalence peaks between 10-20 years of age and is greater among young men. With increasing age the difference in prevalence between the sexes disappears. In the USA about 20% of 20 years olds have allergic rhinitis[4]. Large-scale population surveys have reported that 20-38% of the patients with allergic rhinitis have episodes of asthma[5]. In an epidemiological study among 6 years olds Wright et al found physician diagnosed allergic rhinitis and positive skin tests in 42% of all children, 32% of these children also had asthma (Figure 1)[6].

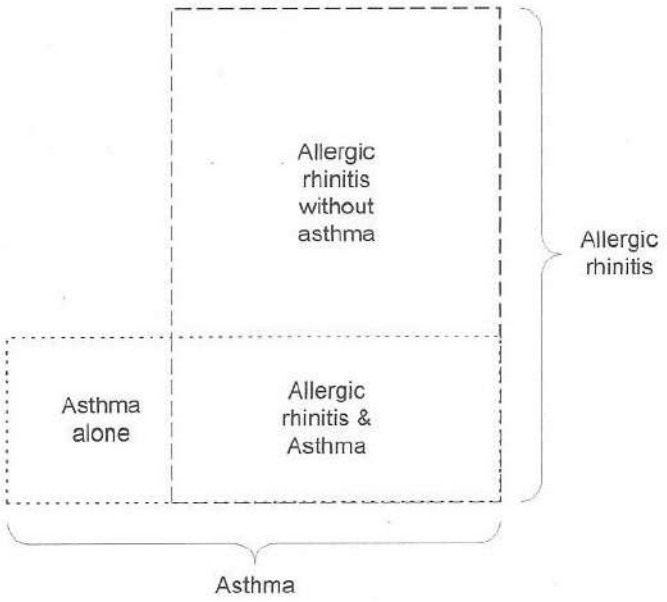


Figure 1: The association between allergic rhinitis and asthma in children at the age of 6 years: one out of three children with allergic rhinitis has asthma, and the majority of children with asthma also has allergic rhinitis[6].

The coexistence of asthma in patients with allergic rhinitis appears to increase; 41% of Italian conscripts with current rhinitis had evidence of asthma in 1983[7], while in 1995 77% of those with current rhinitis also had asthma (Figure 2). In Belgian conscripts the prevalence of reported asthma increased threefold between 1978 and 1991 with an equal increase in airway hyperresponsiveness[8]. Part of the increased prevalence can be attributed to increased recognition of asthma or changes in diagnostic labelling. However, the simultaneous increase of diagnosed asthma and airway hyperresponsiveness supports the hypothesis that there is a true increase in target organ disease, probably secondary to increasing rates of allergic sensitisation. This increase appears to be greatest in children, teenagers and young adults. Prevalence and degree of sensitisation were shown to peak in young adults, regardless of

the allergen, and to diminish with age[9]. Sensitisation to indoor allergens in atopic rhinitic patients was strongly associated with asthma[10].

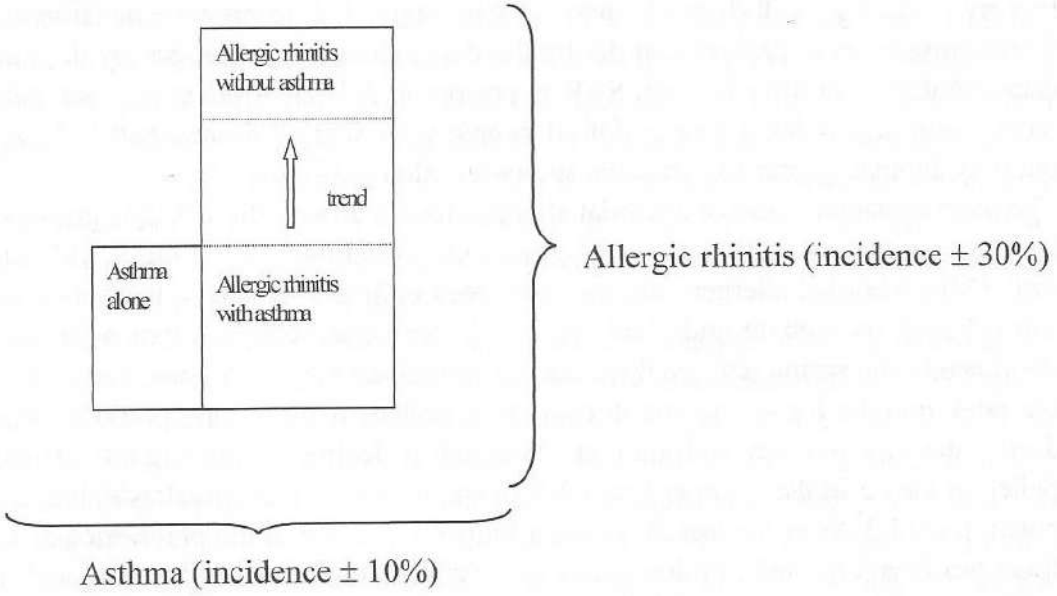


Figure 2: The coexistence of asthma in young adults with allergic rhinitis is increasing[7].

The prevalence of asthma, based on clinical symptoms, in children is approximately 11% in the Netherlands [11]. Worldwide the prevalence of asthma closely follows that of rhinitis but is up to three times lower[12,13]. The average incidence of allergic rhinitis in patients with asthma is high (50-90%[1,6,14], Figure 1). The incidence tends to be higher in younger age groups[6]. New diagnosis of probable allergic rhinitis or asthma were two- to fourfold higher among persons who previously had one of these diseases compared with persons who had no history of either disease [4]. Several cross-sectional studies with both allergic rhinitis and asthma patients suggest that nasal symptoms frequently (59%-74%) start first or in the same year as asthmatic symptoms[2,15]. Other studies did not observe this sequence[4,5].

Allergic rhinitis is a significant risk factor for the development of asthma. Settipane et al reported the results of a prospective 23-year follow-up study involving 690 college students in the United States[16]. Of those with allergic rhinitis 10.5% developed asthma during the study period, compared with 3.6% of students without allergic rhinitis[16]. In a 20-year follow-up study of atopic children, Rackemann and Edwards found that approximately 20% of patients with an allergic rhinitis subsequently developed asthma[17]. Prieto et al calculated an asthma onset rate of 2.5% per year in a patient with allergic rhinitis[18]. In the Tucson Children's Respiratory study 747 children were followed-up from birth. Those who developed allergic rhinitis in the first 2 years were more likely to have asthma by the age of 6 years than the children without allergic rhinitis[6].

In summary the majority of young patients with asthma also has allergic rhinitis. In patients with allergic rhinitis the co-existence of asthma seems to be rising.

2.2 Seasonal allergic rhinitis

Seasonal allergic rhinitis (SAR) is characterised by a history of specific symptoms occurring during well-defined seasons with extended asymptomatic intervals. Symptoms are more pronounced during the day, increase on clear, breezy days and decrease during or after rainfall. SAR is present in 5-10% of the population being more common in young people. Of all people with allergic rhinitis half has SAR, but only about a quarter has seasonal symptoms alone[19] (Figure 3).

The most common cause of seasonal allergic rhinitis around the world is grass pollen. Approximately 9,000 species of grass exist covering 20% of the world's surface. Other seasonal allergens are tree and weed pollen. The start of the pollen season depends on climate and plant species. In temperate climates tree pollen predominate in the spring and are the cause of springtime hay fever. June and July are the peak months for symptoms due to grass pollen, while weeds produce pollen during the late summer and autumn. Although a decline in the amount of grass pollen in the air in the summer (probably due to a reduction of grasslands) has been noted in the UK over the last 30 years, a fourfold increase in the prevalence of hay fever has been reported[1]. Pollen grains are normally impacted on the nasal and nasopharyngeal mucosa after inhalation. Only a small number of airborne pollen grains (1-2%) can penetrate into the lower regions of the respiratory tract[20]. However, in some patients with SAR asthmatic symptoms increase during the grass pollen season (hay asthma) paralleled with an increase in airway hyperresponsiveness. Only a weak relationship between nasal and asthmatic symptoms and the daily pollen concentration in the air has been observed[20-24]. The pathogenesis of hay asthma is unclear. Platts-Mills et al suggested that there is gradual cumulative effect by the deposition of small amounts of pollen in the lower airways eventually leading to a protracted inflammatory reaction[25]. Another proposed mechanism of the pathophysiology of hay asthma comes from the observation that rain can release intracellular allergens from rye grass pollen by osmosis, small enough (< 3 micron) to enter the lung[26]. Allergenic activity has been demonstrated in air-samples, that had passed filters with a diameter much smaller (0.3-1m) than grass-pollen[27]. Similar events could occur outside the laboratory, when floating water-aerosols meet solid particles with allergenic activity (for instance ventilation in the upper airways or by the wind blowing through the grass).

In summary half of the people with allergic rhinitis have SAR. A proportion of these people has a seasonal increase in asthmatic symptoms. The exact mechanism for this phenomenon is unclear.

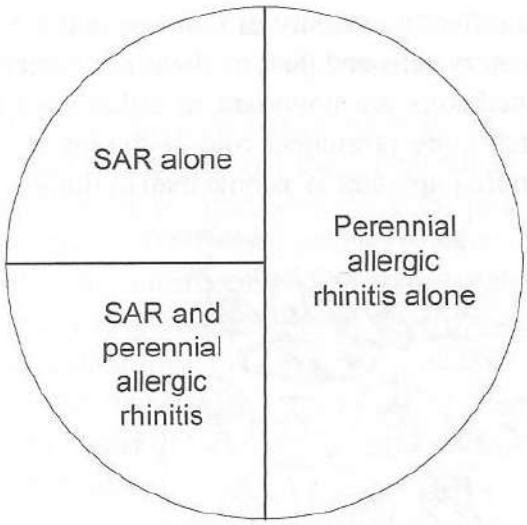


Figure 3: Incidence of seasonal allergic rhinitis (SAR) associated with perennial allergic rhinitis

2.3 Differences between asthma and allergic rhinitis

The anatomy and histology of the upper and lower airway differ. The nose has a predominantly rigid skeleton lined by the nasal mucosa. The vasculature of the nasal mucosa consists of arterial vessels ending in subepithelial and glandular capillary beds. These capillaries are fenestrated and drain into venous sinusoids acting as capacitance vessels. If these vessels are engorged mucosal thickness and upper airway resistance will increase[28]. The capillary bed can be bypassed when blood shunts from the arterial to the venous system through arterio-venous anastomoses. Swelling of the mucosa results in apposition of adjacent surfaces, loss of ciliary action and development of neurogenic contact inflammation[29]. A similar system of venous sinusoids is present in the trachea, although to a lesser extent, but is not found in the bronchi. In the bronchi arteries derived from the bronchial circulation form a dense peribronchial plexus of interconnecting vessels, surrounding and nourishing the airway wall. Branches of these arteries penetrating the muscular layer form a second plexus in the mucosa. Due to this anatomical arrangement anything that causes capillary engorgement and/or leakage can directly alter airway wall geometry. The bronchial and pulmonary circulation anostomose freely throughout the tracheobronchial tree, connecting internal and external capillary networks in the bronchi directly to the left side of the heart [30].

Finally the lower, but not the upper airway is surrounded by smooth muscle, leading to a different mechanism of airway obstruction. In the nose mucosal swelling, mainly due to vascular engorgement, and retained secretions contribute to nasal obstruction[32,33]. In the lower airways a combination of smooth muscle contraction, oedema formation, increased mucus production, and increased airway wall thickness cause airway obstruction[34].

A consequence of the different anatomy in the nose and the lungs is that the residence time of inflammatory cells and their mediators is longer in the lungs. It is also likely that different mediators are important in asthma versus rhinitis. Histamine appears to play a much more prominent role in rhinitis than in asthma, and leucotrienes seem to be more important in asthma than in rhinitis.

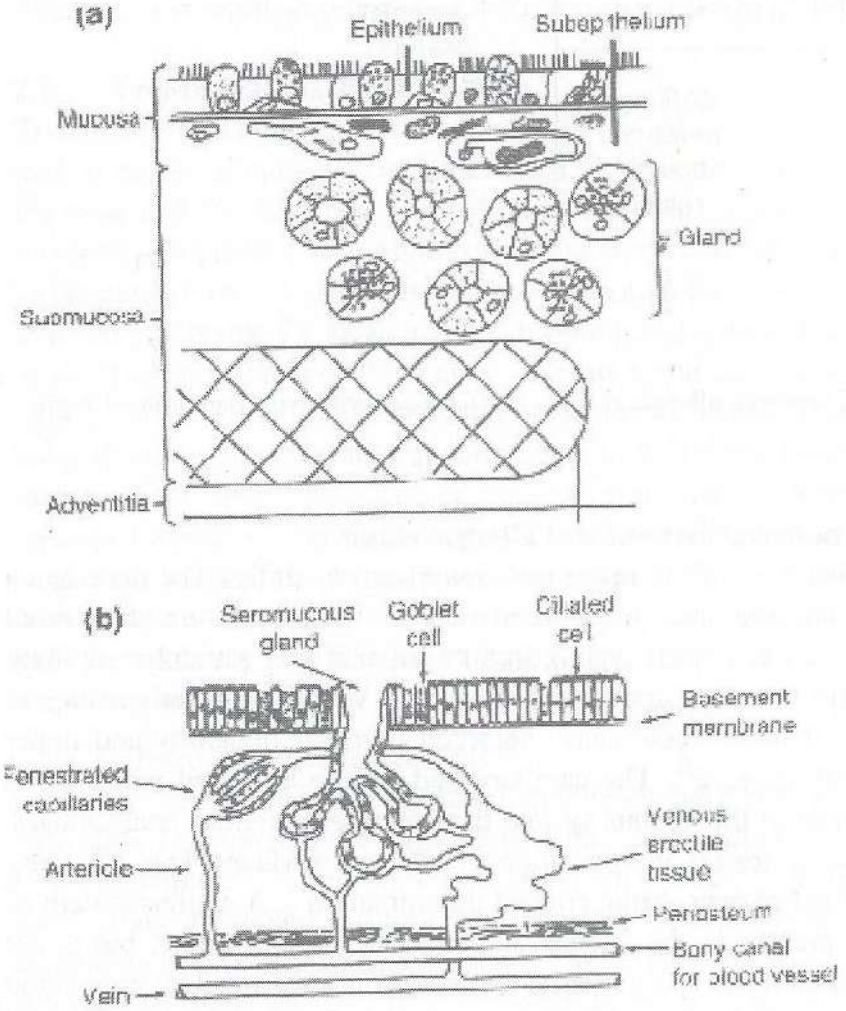


Figure 4: Structure of upper and lower airway mucosa (resp. b and a).

Besides the anatomical differences there is a distinct difference between allergic rhinitis and asthma in the morphology of the inflammatory process. In asthma there is epithelial disruption and thickening of the basement membrane with abnormal collagen leading to airway remodelling. This does not occur in allergic rhinitis[31]. The nose and the lungs respond in different ways with respect to the late phase reaction. In the nose the late phase reaction is considerably weaker than the early phase reaction, while in asthma the late phase reaction is often more severe than the early asthmatic response[35,36].

2.4 Allergic rhinitis and airway hyperresponsiveness

About half of the patients with allergic rhinitis show airway hyperresponsiveness (Figure 5). Of the patients with allergic rhinitis and airway hyperresponsiveness about half has asthma[5,7,8]. Thus about one out of three non-asthmatic subjects with allergic rhinitis has airway hyperresponsiveness to pharmacological stimuli[37,38]. The incidence of airway hyperresponsiveness and asthma in subjects with allergic rhinitis can increase during episodes of increased exposure to allergens[39]. In asthma the interrelationship between airway inflammation and airway hyperresponsiveness has been suggested[40]. However, very little is known about the pathogenesis of airway hyperresponsiveness associated with allergic rhinitis.

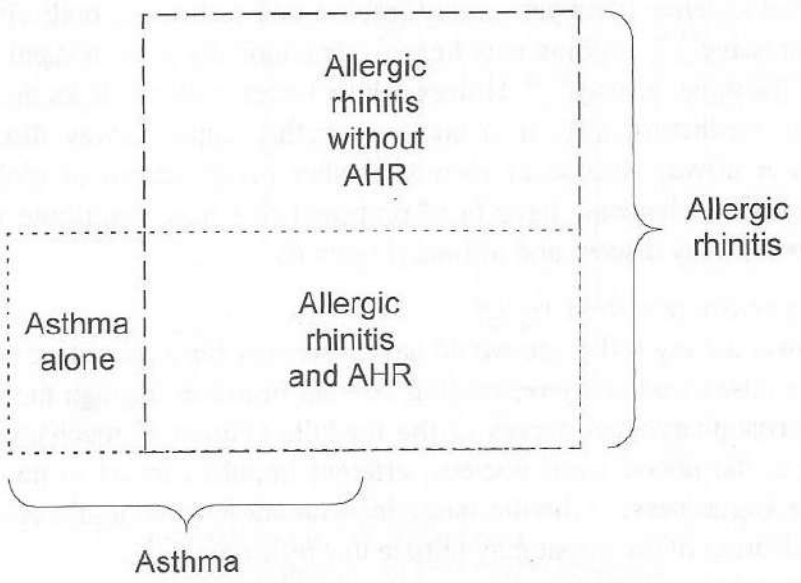


Figure 5: Airway hyperresponsiveness (AHR) in patients with allergic rhinitis

Several investigators have suggested that bronchial inflammation is involved in the pathogenesis of airway hyperresponsiveness in non-asthmatic patients with allergic rhinitis. Foresi et al found inflammatory cells, mast cells and eosinophils, in induced sputum of non-asthmatic patients with SAR and airway hyperresponsiveness, even outside the pollen season[41]. The number of inflammatory cells was intermediate compared to that found in non-asthmatic patients with SAR without airway hyperresponsiveness and patients with asthma[41]. They found a weak but significant correlation between the number of mast cells and eosinophils in sputum and the airway responsiveness to metacholine. Another indication of subclinical bronchial inflammation in non-asthmatic patients with allergic rhinitis and airway hyperresponsiveness is the observation that these patients have daily peakflow rate variation similar to that found in patients with mild asthma[42,43]. Bonavia et al compared airway hyperresponsiveness to inhaled allergen in non-asthmatic subjects with allergic rhinitis to the airway hyperresponsiveness to inhaled allergen in asthmatic subjects[44]. Non-

asthmatic subjects with allergic rhinitis had a positive bronchial response to inhaled allergen, but to a lesser extent than asthmatic subjects had[44]. Another difference they observed was that asthmatics more frequently had a late asthmatic response, when challenged with house dust mite, than subjects with allergic rhinitis alone[44]. They suggested that the difference in symptoms between allergic asthmatics and patients with allergic rhinitis relies on a quantitative difference in airway hyperresponsiveness to allergen.
In conclusion there is evidence of subclinical bronchial inflammation in non-asthmatic patients with allergic rhinitis and airway hyperresponsiveness.

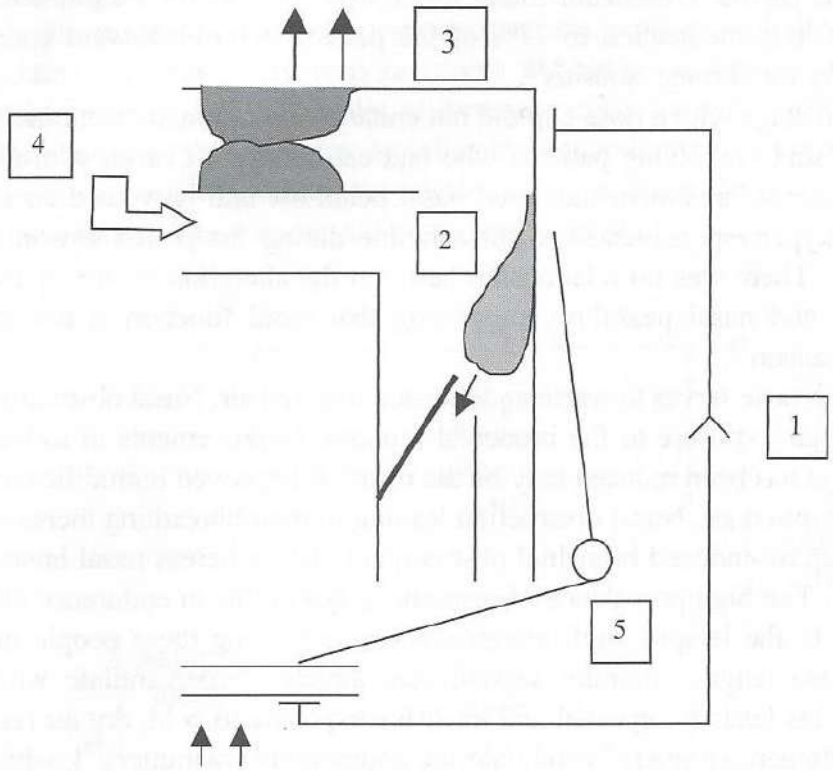
2.5 Mechanisms of disease association

Diseases of the upper respiratory tract have been associated with asthma for a long time. The co-incidence of upper airway disease and asthma in both children and adults is impressive[45-48]. Asthma may improve dramatically after medical or surgical treatment of the upper airway[49-54]. However little direct evidence links the upper and lower airway mechanistically. It is unclear whether upper airway disease is the cause of lower airway disease or merely another manifestation of global airway disease. Several mechanisms have been proposed that may contribute to the link between upper airway disease and asthma (Figure 6).

2.5.1 Upper-lower airway reflex

An upper-lower airway reflex arc would have a sensory limb consisting of receptors in the nose, sinuses, and pharynx, sending afferent impulses through the trigeminal, facial and glossopharyngeal nerves to the medulla (Figure 6, mechanism 1). Via connections to the dorsal vagal nucleus, efferent impulses travel to the lower airways by the vagus nerve. Chronic nasal inflammation, post-nasal secretions and continuous clearing of the throat may initiate this reflex arc.
In animals stimulation of the nasal mucosa has been shown to cause reflex bronchoconstriction[55], reflex bronchodilatation[56] or no change in lower airway function. The type of reaction depends on the type of animal and stimulus selected[57]. Nadel and Widdicombe found that only mechanical irritation of the larynx, not of the nose, in cats led to bronchoconstriction[57]. The existence of a naso-bronchial reflex in humans has been demonstrated by several studies using nasal silica application[58] or petrolatum packing[58] as the provocative substances. Both systemic administration of atropine[58] as well as resection of the trigeminal nerve[60] blocked the bronchospasm induced by nasal silica, suggesting that a cholinergic reflex caused the effect. Similarly Nolte and Berger showed that a cold stimulus to the nose can induce rapid-onset bronchoconstriction[61]. In a study of Yan et al 12 persons with perennial rhinitis and stable asthma were challenged with nasal histamine. It was observed that FEV_1 was reduced by 10% or more immediately after provocation in 8 out of 12 patients[62]. However several other studies failed to detect changes in pulmonary function using histamine[63-65] or allergen[63-66] as the challenge material. Although nasal allergen provocation had no direct effect on bronchial calibre it increased airway hyperresponsiveness to metacholine as early as 30 minutes after challenge

and persisting for another four hours[66]. These rapid changes suggest a neural reflex mechanism.



Legend:

1	Upper to lower airway reflex arch
2	Pulmonary aspiration of post-nasal secretions
3	Systemic absorption of inflammatory mediators from the upper airway inducing lower airway inflammation
4	Impaired nasal function by nasal blockage leading to mouth breathing
5	Inflammatory reflex via lymph circulation

Figure 6: Mechanisms of association between upper airway disease and asthma.

2.5.2 Impaired nasal function

The nose is the outermost part of the respiratory tract and a protective barrier against inhalants, such as aeroallergens and noxious substances. The prime function of the nose is to filter and adjust inspired air to bodily conditions before it enters the lower airways. Nasal blockage as a result of tissue swelling and retained secretions may cause a shift from nasal to predominantly mouthbreathing. The lower airways will be exposed to a higher influx of air-particles of allergic and non-allergic origin, increasing the allergen load to the lungs. In susceptible persons this may lead to inflammatory changes and an increase in airway hyperresponsiveness.

Slavin et al described that asthma symptoms improved in 66% of patients from whom nasal polyps were surgically removed[52]. In a study of Stoop et al airway

calibre (FEV_1) increased 10% in 63% of patients with a chronic upper airway obstruction due to nasal polyps six months after they had endoscopic sinus surgery for nasal polyps[67]. However, patients received intranasal corticosteroid (400(g budesonide) in this period. Hosemann found an improvement in the lungfunction and/or less use of lung medication in 77% of the patients who underwent endoscopic sinus surgery for chronic sinusitis[68].
Complete nasal blockage with a nose clip did not enhance the asthmatic response to cat allergens in a study involving patients who had cat allergy[69]. Corren et al observed that nasal steroid treatment increased nasal peakflow and prevented an increase in airway hyperresponsiveness to metacholine during the pollen season in mild asthmatics[70]. There was no relationship between the alteration of airway hyperresponsiveness and nasal peakflow, suggesting that nasal function is not the single major mechanism[70].
Besides filtering the nose serves to warm and moisten inspired air. Nasal obstruction leads to cold, dry air exposure to the bronchial mucosa. Improvements in asthma after nasal blockage has been reduced may be the result of improved humidification and warming of inspired air. Nasal obstruction leading to mouthbreathing increases the severity of exercise-induced bronchial obstruction (EIB), whereas nasal breathing reduces EIB[71]. The high prevalence of respiratory symptoms in endurance athletes may be due to the lengthy high intensity exercise training these people undergo. During these lengthy training sessions the athletes hyperventilate while mouthbreathing. This leads to repeated and intensive exposure to cold, dry air (skiers [72,73]), pollen allergens (runners[74]) and chlorine compounds (swimmers[75]), which may induce or enhance lower airway inflammation and airway hyperresponsiveness. The type of airway inflammation found in athletes is, however, different from the airway inflammation in allergic patients.

2.5.3 Pulmonary aspiration of post-nasal secretions

Inflammation of the mucous membranes of the upper airway leads to the passage of mucopurulent secretions (post-nasal drip) into the pharynx. These post-nasal secretions, containing inflammatory cells (and their products) and infectious seeds, are to some extent aspirated and may therefore play a significant role in the association between pulmonary and upper airway disease. Aspiration occurs only in patients with depressed consciousness and cough reflexes[76] and post-nasal secretions mainly go to the stomach. However, Huxley et al showed aspiration of radionuclide instilled in the nasopharynx in 70% of patients with depressed consciousness and in 45% of healthy subjects[77].
Induction of a sterile nasal/sinus infiltrate in an animal model of rhinosinusitis resulted in increased lower airway hyperresponsiveness to histamine[78]. This increase in airway hyperresponsiveness was prohibited by strategies that blocked drainage of nasal secretions into the lower airways such as intubation and head down positioning. When the rhinosinusitis was induced after granulocyt depletion of the animal no increase in airway hyperresponsiveness was found. Thus eosinophils and neutro-

phils and/or their products (inflammatory mediators or chemotactic factors) appeared to be required for the increase in airway hyperresponsiveness.

2.5.4 Reabsorption of inflammatory mediators from the upper airway

Inflammatory mediators are absorbed from the inflammatory process in the upper airway into the circulation. It can be speculated that these mediators reach the lining of the lower airways and give rise to an interaction the upper and lower airway.
In an animal model of rhinosinusitis, induction of a sterile nasal/sinus infiltrate resulted in increased airway responsiveness to histamine[78]. A site of inflammation induced in a similar way distant from the lungs or the nasal/sinus infiltrate anatomically disconnected from the lungs could not induce airway responsiveness, suggesting that systemic absorption of inflammatory mediators was not likely an important mechanism in this model.
Corren et al investigated the effect of nasal allergen challenge on lower airway responsiveness[66]. Nasal allergen challenge induced immediate and late increases in airway hyperresponsiveness. Corren et al speculated that the immediate alteration in airway hyperresponsiveness can be explained by either a neural reflex or inflammatory mediators released into the systemic circulation[66]. They concluded that the change in airway hyperresponsiveness 4.5 hours after nasal challenge was incompatible with a neural mechanism and suggested the late increase in airway hyperresponsiveness reflected more likely the action of inflammatory mediators reaching the lower airways either through post-nasal drip or via the systemic circulation.

2.5.5 Inflammatory reflex between the upper and lower airway

Antigen presenting cells, such as Langerhans cells, may be involved in a connection between the upper and lower airway. Allergens that are deposited on the nasal mucosa are thought to be processed by antigen presenting cells[79]. These cells may travel to the regional lymph nodes where they present allergen to naive Th_0 lymphocytes, which differentiate into Th_2 lymphocytes. The Th_2 lymphocytes may migrate to the mucosa of the lower airways linking upper airway inflammation to the lower airway[80]. As the lower and upper airway mucosa have the same constitution patients with allergic asthma will in principle respond on allergen presented in the nose. It has been demonstrated that the number of antigen presenting cells is increased following allergen exposure and is markedly reduced by topical steroids[81]. In a recent study Greiff et al found that orally inhaled budesonide at a daily dose of 600 µg reduced the seasonal eosinophilia both in the circulation and in the nose, along with an attenuation of seasonal nasal symptoms in patients with seasonal allergic rhinitis without asthma. They suggested a systemic effect of the orally inhaled steroid was likely to be the responsible mechanism for the effect. However, it can be speculated that an inflammatory reflex was the cause of the effect[82].

Studies with both animal and human subjects have explored the probable mechanisms linking the upper airway and asthma. Naso-bronchial reflexes, persistent nasal dysfunction (leading to chronic exposition of the lower airways to unconditioned air) and pulmonary aspiration of nasal secretions may all contribute to lower

airway dysfunction in patients with upper airway disease. The importance of nasobronchial reflexes to asthma is likely to be small. (However, a subpopulation of asthmatics may have active nasobronchial reflexes). There is no evidence that reabsorption of inflammatory mediators plays a major role in the link between the upper and lower airway. We need further studies to elucidate the roles of impaired nasal function, post-nasal secretions and inflammatory reflexes on asthma.

2.6 Treatment of allergic rhinitis

Treatment of allergic rhinitis can be either topical or systemical. For topical treatment a variety of intranasal drugs are used. For adequate penetration of the drug into the nose and for the prevention of nasal bleeding the technique of application is important. Deposition of an intranasal drug should be preferentially on the swollen turbinates, which cause the obstruction, and not on the septum. The septal mucosa is thin and vulnerable for ulceration and bleeding and does not substantially contribute to nasal obstruction. For this reason patients using intranasal spray should be instructed not to spray on the septum but on the turbinates. This can be achieved by using the right hand for the left naris pointing the nozzle towards the left ear at actuation of the spray and vice versa for the right naris. Severe septal deviation or swollen turbinates may impede direct delivery of topical agents and necessitate surgical correction and topical vasoconstrictors respectively. Compliance to topical prophylactic treatment of allergic rhinitis may be compromised by the relatively slow therapeutic onset of action of these drugs, compared to topical vasoconstrictors such as xylomethazoline.

2.6.1 Intranasal corticosteroids

Currently used steroids for intranasal application have potent vasoconstrictor activity (Table 1). Comparative trials showed that intranasal corticosteroids are superior to antihistamines[83-85] and intranasal cromolyn sodium [86] in relieving nasal symptoms. They are especially more effective on nasal blockage[85,87]. A reduction of symptoms is to be expected in 2-7 days[88]. Maximum improvement is attained after 2 weeks. Parents of children may complain of noisy nasal breathing at the start of therapy. This can be a sign of an imminent restoration of nasal breathing, as children will breathe through their nose if they have the opportunity[89]. Short-term comparative studies in allergic rhinitis have shown relatively little difference between the various intranasal corticosteroids[90-93]. Fluticasone aqueous spray 200 μg once daily was as effective as Beclomethason aqueous spray 168 μg twice daily in a large placebo controlled study (300 patients). However, a one-year comparison study indicated that long term use of Fluticasone is superior to Beclomethason[92]. It was observed that Fluticasone 200 μg once daily in the morning was as effective as the same daily dose taken in two doses[94], although there was significantly less nasal itching and eye symptoms in the twice-daily regimen[95].

Several studies have shown that long-term therapy with intranasal corticosteroids is virtually without systemic effects in adults[96-98]. One study reported bilateral subcapsular cataracts in 21 patients possibly associated with intranasal or inhaled steroid

use. However, most of the patients used the preparation in higher than recommended doses, and 9 of the 21 patients also received systemic corticosteroids[99]. One controlled study showed an inhibition of short-term lower leg growth in children with allergic rhinitis using intranasal budesonide in a regular dose (400μg)[100]. A subsequent study of the same investigators showed no short-term inhibition of lower leg growth with 200μg and 400μg of intranasal budesonide[101]. Systemic side effects, such as Cushing's syndrome, of overuse of intranasal Beclomethason have been observed[102,103]. There is no pulmonary route for systemic absorption of an intranasal aqueous spray as particles are too large (30 micron) to penetrate into the lungs (respirable range < 5-10 micron [104,105]).

Local side effects of intranasal steroids, such as irritation, burning and reactive sneezing are generally minor and local and usually disappear after several days[106]. After several weeks of continuous use of intranasal corticosteroids dryness in the nose may be felt and crusting may appear[106]. This can be largely avoided by using sprays with an aqueous base. Ulceration of nasal mucosa may develop leading to bleeding of nasal mucosa in 5-10% of patients[107]. A few reports of septal perforation after usage of intranasal corticosteroids have been published[108]. No histopathological changes have been found in biopsies of the nasal mucosa[109,110] after prolonged therapy with Beclomethason.

Table 1: Intranasal corticosteroids: relative topical potencies

Agent	Topical vasoconstrictor activity
Hydrocortisone	1
Triamcinolon acetonide	1000
Beclomethasone dipropionate	5000
Budesonide	10.000
Fluticasone propionate	10.000

Data from Siegel SC. Topical intranasal corticosteroid therapy in rhinitis. J Allerg Clin Immunol 1988;81:984-91. And Phillips GH. Structure activity relationships of topically active steroids: the selection of fluticasone propionate.Resp Med 1990;84(Suppl A):19-23.

2.6.2 Antihistamines

Antihistamines compete with histamine at its receptor sites on nerve endings, glandular cells and smooth muscle. The side effects of antihistamines, such as central nervous system (CNS) depression, dry mouth, constipation, tachycardia are not related to histamine receptor antagonism but due to their anticholinergic properties. In children anthistamines can occasionally stimulate the CNS[111]. Second generation antihistamines, such as terfenadine, astemizol, loratadine, cetirizine and acrivistine, do not cross the blood-brain barrier at therapeutic doses and therefore cause less sedation[112-114]. Studies have shown that the newer antihistamines are effective in 67% of patients with seasonal rhinitis[115] and are as effective as the older agents[116,117]. Loratadine one of the newer agents can inhibit the release of histamine[118,119] and inhibit eosinophil activation[120]. The use of antihistamines, whether orally or topically applied, is an appropriate mode of treatment in patients with

intermittent and mild symptoms such as sneezing, itching and rhinorrhoea. Nasal blockage however is only slightly effected[121-123]. Intranasal corticosteroids are more effective than antihistamines in patients with persistent symptoms of allergic rhinitis [83]. The addition of a vasoconstrictor to an antihistamine can provide nasal relief comparable to the use of topical steroids[124]. It has been shown that the combination of antihistamines and intranasal corticosteroid therapy can give consistently better relief of nasal symptoms than the separate use of the drugs[125,126]. Especially when allergic rhinitis is associated with a conjunctivitis and palatal itch, which happens frequently with seasonal allergic rhinitis, antihistamines may be effectively combined with intranasal steroid[127].
Cardiac arrhythmics have been reported with the second-generation antihistamines terfenadine and astemizole, when serum drug levels are greatly elevated[128,129]. No such effects have been revealed by dose-response studies with loratadine and cetirizine[130,131].

2.6.3 Cromones/vasoconstrictors/anticholinergics

Sodium cromoglycate is thought to stabilise the sensitised mast cells and prevent the degranulation and mediator release in the allergic response[132]. Intranasal cromoglycate is significantly better than placebo for the treatment of all symptoms of both seasonal and perennial allergic rhinitis[133,134] but is inferior to intranasal corticosteroid in controlling all nasal symptoms[86]. The symptoms of sneezing, rhinorrhoea and pruritus are usually better controlled than nasal obstruction[135].
There are two groups of sympaticomimetic agents with vasoconstrictive activity that are used intranasally. Catecholamines, such as ephedrine, and imidazoline derivatives, such as xylomethazoline. These vasoconstrictor agents do not reduce rhinorrhea, sneezing or nasal pruritus[136], but can improve the penetration of intranasal maintenance medication in case of markedly swollen turbinates.
Intranasal anticholinergics such as ipratropiumbromide are effective in controlling the excessive watery rhinorrhea associated with neurogenic stimuli (e.g. cold air, spicy foods) of the mucosal glands that take place in the chronic inflammation[137]. However they have no effect on nasal blockage, sneezing, itching and ocular symptoms[138].

2.7 Conclusion

The association between asthma and allergic rhinitis is strong, which is expressed by a high concurrence (80-90%) of allergic rhinitis in children with asthma and a rising co-existence of asthma in patients with allergic rhinitis.
Additionally in patients with asthma without symptoms of allergic rhinitis eosinophillic inflammation of the nasal mucosa has been found, and subclinical bronchial inflammation has been demonstrated in patients with allergic rhinitis but no evident asthma. The strong epidemiologic association between allergic rhinitis and asthma may be purely explained by the fact that the upper and lower airway are lined by the same epithelium and have the same exposure to inhaled noxes. However, there may be a mechanical link between the two diseases as well. Studies with both animal and

human subjects have explored the probable mechanisms linking the upper airway and asthma. Naso-bronchial reflexes, impaired nasal function (leading to chronic exposition of the lower airways to unconditioned air) and pulmonary aspiration of post-nasal secretions may all contribute to lower airway dysfunction in patients with upper airway disease.

Although the epithelium and the specific hyperresponsiveness to stimuli is similar in the upper and lower airway there is a distinct difference in the morphology of the inflammatory process in allergic rhinitis and asthma. In asthma there is epithelial disruption and thickening of the basement membrane with abnormal collagen leading to airway remodelling. This does not occur in allergic rhinitis. Furthermore the nose and the lungs respond in different ways with respect to the late phase reaction. In the nose the late phase reaction is considerably weaker than the early phase reaction, while in asthma the late phase reaction is often more severe than the early asthmatic response.

Regarding the therapy of allergic rhinitis, comparative trials have shown that intranasal corticosteroids are superior to antihistamines and intranasal cromolyn sodium in relieving nasal symptoms. They are particularly more effective in reducing nasal obstruction. This facilitates the entry of warmed, humidified and filtered air into the lungs, which is potentially beneficial to the lower airway.

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3

Effect of intranasal corticosteroid on symptoms of asthma

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Systematic Review for the Cochrane Library

3.1 Summary:

Allergic rhinitis often co-exists with asthma and has been proposed to be linked to it. Using a systematic approach, the medical literature was thoroughly searched to find studies, which looked at the effects of treating allergic rhinitis with intranasal steroids on asthma. The studies were assessed for quality to ensure that only studies that were unbiased were included in the review to limit the potential for a bias. Two independent reviewers assessed each paper for quality and extracted data. The results of the studies were combined to see if treating allergic rhinitis with intranasal steroids makes a difference to asthma symptoms and lung function. There was a moderate improvement in asthma symptoms in patients with mild asthma and allergic rhinitis. Lung function did not improve under therapy with intranasal corticosteroids.

3.2 Abstract

Background:

Allergic rhinitis is characterised by a history of specific symptoms such as sneezing, rhinorrhoe and pruritus, occurring during periods of exposure to allergens. Asthma frequently co-exists with allergic rhinitis and has been associated with it. The best current therapy for allergic rhinitis is intranasally deposited steroids. Intranasal steroids may have a beneficial influence on symptoms of asthma in patients with allergic rhinitis and asthma by reducing the inflammatory process in allergic rhinitis.

Objectives:

The severity of allergic rhinitis may influence asthma, so the objective of this review was to evaluate the effectiveness of treatment for allergic rhinitis with intranasal steroid in terms of its benefit on asthma.

Search strategy:

The Cochrane Airways group trials register, Medline, Embase, Handsearching.

Selection criteria:

Randomised controlled trials of treatment for allergic rhinitis with intranasal steroids in adults and children with a diagnosis of both asthma and allergic rhinitis.

Data collection & analysis:

Trial quality and data extraction were carried out by two independent reviewers. Authors were contracted for confirmation or more data.

Main results:

Four trials met the inclusion criteria. Intranasal steroids used were either beclomethasone or budesonide and were given with an aqueous pump spray. Treatment duration ranged from 4 to 6 weeks. In two studies using intranasal steroid had a significant effect on symptoms of asthma. In the other two studies a trend of less asthma symptoms was seen.

Reviewers' conclusions:
In subjects with mild asthma and allergic rhinitis there was a moderate improvement of symptoms of asthma following treatment of allergic rhinitis with intranasal steroids. There was no improvement of airway calibre (FEV_1).

3.3 Background

Disorders of the upper respiratory tract have long been associated with asthma. The co-incidence of upper-airway disease, such as allergic rhinitis, sinusitis and nasal polyps, in both children and adults is impressive. [1,2]

The prevalence of allergic rhinitis and asthma has increased [3] over the last decennia, probably secondary to increasing rates of allergic sensitisation. Sensitisation to indoor allergens in atopic rhinitic patients was strongly associated with asthma[4]. World-wide the prevalence of asthma closely follows that of rhinitis but is up to three times lower [5,6] The average incidence of allergic rhinitis in patients with asthma is high (50-90%).[7-9] The concurrence tends to be higher in younger age groups.[9] Several studies have shown that allergic rhinitis is a significant risk factor for the development of asthma.[10-12]

Studies with both animal and human subjects have explored the mechanisms underlying the link between the upper airway and asthma. Naso-bronchial reflexes, persistent nasal dysfunction (leading to chronic exposition of the lower airways to unconditioned air) and pulmonary aspiration of nasal secretions have been proposed to contribute to lower airway dysfunction in patients with upper airway disease. However, there is no direct evidence linking allergic rhinitis and asthma mechanistically.

Intranasal corticosteroids are effective in relieving nasal symptoms of allergic rhinitis. They are more effective compared to other therapy on nasal blockage.[13,14] A reduction of symptoms is to be expected in 2-7 days.[15] Maximum improvement is attained after 2 weeks. Short-term comparative studies in allergic rhinitis have shown relatively little difference between the various intranasal corticosteroids[16-19]. Fluticasone aqueous spray 200 mcg once daily was as effective as Beclomethason aqueous spray 168 mcg twice daily in a large placebo controlled study (300 patients).

The first data on the efficacy of intranasal corticosteroids on lower airway physiology in asthmatic patients with allergic rhinitis were in the study of Henriksen et al in 1984[20]. They showed that intranasal budesonide not only improved nasal symptoms, but also decreased asthmatic symptoms and the severity of exercise induced bronchoconstriction (EIB) in asthmatic children with perennial allergic rhinitis. Welsh et al demonstrated that intranasal corticosteroids prevented the increase seasonal asthma symptoms in asthmatic adults with seasonal allergic rhinitis[21]. Watson et al found a trend of less asthmatic symptoms in asthmatic children and adolescents with perennial allergic rhinitis after treatment with intranasal steroids[22]. Corren et al

treated asthmatic adults with seasonal allergic rhinitis with intranasal steroids during the ragweed season and observed a trend of less asthma symptoms.[23]

It has been suggested that the beneficial influence of intranasal steroid on the lower airway is due to a restoration of the nasal function leading to an improvement of air conditioning (i.e. filtering, warming and humidifying the air). Other proposed mechanisms are a reduction of aspiration of post nasal-secretions, an alleviation of upper-lower airway reflexes or a reduction of reabsorption of mediators or chemotactic factors from the inflammatory process in nose or sinuses.

Objectives:
The objective of this systematic review was to evaluate the effect of intranasal corticosteroid on asthmatic symptoms and lung function in asthmatic patients with allergic rhinitis.

Criteria for considering studies for this review

Types of studies:
Randomised double-blind placebo-controlled, parallel and cross-over group, trials studying the influence of intranasal steroids in asthmatics with allergic rhinitis.

Types of participants:
Asthma: History of reversible symptoms of lower airway obstruction in children and adults.
Allergic rhinitis: History of symptoms of rhinitis provoked by exposure to allergens (seasonal and/or perennial) in children and adults and positive skin test and/or specific IgE to inhalant allergy.

Types of interventions:
Intranasal deposited corticosteroid for a period of 4 to 6 weeks.

Types of outcome measures:
The following outcomes were evaluated
Asthma symptoms and lung function measured as Forced Expiratory Volume in one second (FEV1).

Search strategy for identification of studies:
The Cochrane Airways Group asthma randomised controlled trial (RCT) register was searched using the terms:
"asthma" AND "intranasal corticosteroids" OR "nasal corticosteroids" OR "intranasal steroids" OR "nasal steroids"
"asthma symptoms" AND "intranasal corticosteroids" OR "nasal corticosteroids" OR "intranasal steroids" OR "nasal steroids"
"asthmatic symptoms" AND "intranasal corticosteroids" OR "nasal corticosteroids" OR "intranasal steroids" OR "nasal steroids"

3.4 Methods of the review

IDENTIFICATION OF RELEVANT STUDIES

All identified abstracts were assessed independently by two reviewers. The full text version of each potential article was obtained for assessment by two independent reviewers to establish whether it met the inclusion criteria. The percentage agreement for inclusion/exclusion of studies was 100%.

QUALITY

Study quality was assessed independently and scored by two reviewers using two instruments. The first, the Jadad system, allows for a score between 0 and 8 with higher scores indicating a better description of the study. The Jadad system measures the clarity of the description of: inclusion criteria, randomisation, adverse effects, blinding, treatment of withdrawals and dropouts and statistical analysis. Studies were further assessed as "Adequate", "Inadequate" or "Unclear" according to the actual methods used for randomisation and concealment of allocation according to the Cochrane system. In this assessment, if studies are either not truly randomised (e.g. alternated) or if allocation to treatment or control groups is not truly blinded, studies are considered "inadequate". If the author does not fully state these methods, the study is characterised as "unclear" until the author is contacted and clarification can be made.

OUTCOMES

The following health outcomes were identified for assessment:
Asthma symptoms score
Lung function: spirometry, measured as forced expiratory volume in 1 second (FEV1)

AUTHOR CONTACT

Authors were contacted to verify and provide further information about methodological approaches and outcomes data.

ANALYSIS

Outcomes were analysed as continuous outcomes, using standard statistical techniques.
The weighted mean difference (WMD) and 95% confidence intervals were calculated.

Description of studies

STUDIES INCLUDED:

The search strategy yielded 217 abstracts of which 10 full text versions of papers were retrieved (table 1). Of these four randomised controlled trials were included (table 2).

Three trials investigated the effect of intranasal beclomethasone dipropionate (Reed 1988, Watson 1993, Corren 1992); one investigated the effect of intranasal budesonide (Henriksen 1984).

PARTICIPANT CHARACTERISTICS:

Number of participants:
The number of participants randomised ranged from 36 (Henriksen 1984) to 18 (Corren 1992).

Age:
Two trials studied adults (Reed 1988, Corren 1992), one trial studied children and adolescents (7-17 years, Watson 1993). One trial studied children 7-15 years (Henriksen 1984). In the adult studies, mean ages were 36 years (Henriksen 1984) and 27 years (Reed 1988).

Diagnostic criteria for asthma:
The following methods were reported as the methods used to diagnose asthma for inclusion of subjects into the respective studies:
Doctor's diagnosis: Corren 1992, Reed 1988
American Thoracic Society guidelines: Henriksen 1984
Canadian consensus guidelines on asthma: Watson 1993

Baseline severity of asthma:
Mild asthma according to the results of the asthma symptom scores and FEV1 % pred >80%: Corren 1992, Reed 1988 and Henriksen 1984.
Mild to moderate asthma according to the results of the asthma symptom scores: Watson 1993.
None of the patients in all studies used inhaled maintenance corticosteroids.

Baseline severity of allergic rhinitis:
Mild allergic rhinitis according to the results of the rhinitis symptom scores: Corren 1992, Reed 1988 and Henriksen 1984.
Mild to moderate allergic rhinitis according to the results of the rhinitis symptom scores: Watson 1993.
None of the patients in all studies used intranasal corticosteroids.
Methodological quality of included studies:
Each study was scored according to the 0-8 point scale of Jadad accompanied by a separate rating of the allocation procedure where A indicates appropriate blinding, B unclear and C, an inadequate allocation procedure.
The range of of Jadad ratings was (), the mean indicating only minimal opportunity for bias among these studies.
The quality ratings for the trials were Corren 1992, Henriksen 1984, Watson 1993

3.5 Results

The four trials investigated the effect of intranasal steroid on asthma in 93 patients. Asthma symptoms were measured and reported in all of the included studies. Studies used different scales. Two studies were incomplete in reporting outcomes (no SD's were given), and this has prevented quantative data synthesis of all four studies being pooled together for analysis of asthma symptoms. We have pooled together the two smaller studies of Corren and Watson accumulating 39 patients to analyze asthma symptoms. In two studies FEV_1 was reported, we pooled these two studies together accumulating 54 patients to analyze effects on airway caliber. Neither of the pooled analyses showed significant heterogeneity. Overall there was a moderate benefit of treatment with intranasal steroid on asthmatic symptoms, but not on lungfunction in mild asthmatic patients with allergic rhinitis.

DATA:

Asthma symptoms

Global asthma symptom score weighted mean difference (95% CI) –0.37 (-0.90, 0.16).

Airway calibre (FEV_1)

FEV1 Standardised Mean Difference (95% CI) -.002 (-0.54,0.54).

3.6 Discussion

In this systematic review of four trials, we found a moderate beneficial influence of the treatment of allergic rhinitis with intranasal steroid on symptoms of asthma in patients with mild asthma. There was no clear effect on lung function, although we only reviewed two studies for that.

The duration of the therapy was short, and it might be argued that a longer period of observation would be necessary before improved control of allergic rhinitis resulted in a stronger effect on asthma symptoms or an increase in airway calibre.

Our original intention had been to look at the effect of treatment with intranasal steroids in both adults and children, and in asthmatics with seasonal and with perennial allergic rhinitis. The paucity of appropriate studies limited the scope of the final review.

Asthma and allergic rhinitis are both common conditions that appear to share the same key elements of pathogenesis. Studies have found a high prevalence of allergic rhinitis in patients with asthma[7-9] suggesting the relationship may be causal. A number of mechanisms could be invoked to explain how treating allergic rhinitis with intranasal steroid could influence asthma[21]. Restoration of the nasal function (air conditioning), reduction of post nasal secretions leading to less pulmonary aspiration of secretions, alleviation of nasal-bronchial reflexes, reduction of reabsorption of inflammatory mediators from the upper airway and an inflammatory reflex all

may contribute to lower airway dysfunction in patients with allergic rhinitis. Intranasal steroids may influence the lower airway by all of these proposed mechanisms.

In most of the studies antihistamines were permitted as rescue medication for nasal symptoms. Histamine type 1-receptor antagonists have been shown to have direct effects on the lower airways. Large-scale trials with second-generation antihistamines have demonstrated a reduction of both nasal and asthma symptoms and an improvement of PEFR.[24,25]

REVIEWERS' CONCLUSIONS

Implications for practice

In subjects who had both mild asthma and allergic rhinitis, treatment for allergic rhinitis with intranasal corticosteroids produced improvement in asthma symptoms. Omission of treating allergic rhinitis may lead to suboptimal results in asthma treatment. However the effect appears to be insufficient to replace pulmonary therapy.

Implications for research

It is recommended that further studies should be performed to identify the effect of prolonged therapy with intranasal steroid on asthma symptoms and airway calibre in asthmatics with allergic rhinitis. Further studies should be performed in patients with allergic rhinitis and moderate and severe asthma to determine the effect in these patient groups.

Table 1 of excluded studies

	Sarti (26)	Wood (27)	Armitage (28)	Aubier (29)	Foresi (30)	Pelucchi (31)
reason for exclusion	no controls	non-asthmatics included	non-asthmatics included	no asthma	no asthma	no asthma

Table 2 of included studies: effect of intranasal corticosteroids on asthma symptoms

Reference N = study subjects, age	**Drug and duration of treatment**	**Daily dose (μg)**	**Seasonal/ Perennial**	**Nasal rescue drugs**	**Asthma Symptoms**
Welsh et al N =21 14-37 yr	Bdp 8 weeks	336	SAR	Antihistamines	↓
Henriksen et al N =36, 7-15 yr	Bud 4 weeks	400	PAR	None	↓
Watson et al N =21 7-17 yr	Bdp 4 weeks	400	PAR	None	Trend of less symptoms
Corren et al N =18, Adults	Bdp 6 weeks	336	SAR	Antihistamine/ ephedrine combination	Trend of less symptoms

Bdp = beclomethasone dipropionate
Bud = budesonide
SAR = seasonal allergic rhinitis
PAR = perennial allergic rhinitis
↓: significant decrease

3.7 References

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4

Influence of intranasal steroids on bronchial hyperresponsiveness during the grass pollen season in children and young adults with asthma and hayfever

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submitted

4.1 Summary:

Background – It has been reported that intranasal corticosteroids can influence BHR in asthmatics with seasonal rhinitis. The purpose of the present study was to evaluate the effect of intranasal fluticasone propionate and beclomethasone dipropionate on BHR and bronchial calibre (FEV_1) in children and young adults with seasonal rhinitis and mild asthma during two consecutive grass pollen seasons.

Methods – In the first pollen season 25 patients, aged 8-28 years were included in a double-blind placebo-controlled study. The active treatment group used fluticasone aqueous spray 200 μg once daily. In the second pollen season 72 patients, aged 8-28 years were included in a double-blind placebo-controlled study. The study-design was similar to the study performed in the previous year, except that an additional treatment group of patients using beclomethasone 200 μg twice daily was included. FEV_1 was measured before and after three and six weeks of treatment, BHR to methacholine (PD_{20}) was measured before and after six weeks of treatment.

Results – In the first season the mean $logPD_{20}$ of the patients decreased significantly both in the fluticasone group (2.43 μg sd 0.8 to 1.86 μg sd 0.85, $p= 0.002$) and in the placebo group (2.41 μg sd 0.42 to 1.87 sd 0.78, $p= 0.01$) without any intergroup difference of the change in $logPD_{20}$ ($p=0.2$). The FEV_1 did not change in the fluticasone group nor in the placebo group. In the second season the mean $logPD_{20}$ in the fluticasone, beclomethason and the placebo group did not change significantly during the pollen season. In the active treatment groups FEV_1 improved significantly after three weeks of treatment, when allergen load was low, but decreased to baseline value at the end of the study period during high allergen load.

Conclusions – Intranasal corticosteroid did not protect against an increase in BHR nor diminished BHR during the grass pollen season in children and young adults with seasonal rhinitis and mild asthma. The change in BHR seemed to depend on the pollen allergen load.

4.2 Introduction

A beneficial influence of intranasal corticosteroid therapy on bronchial hyperresponsiveness (BHR) in patients with a seasonal allergic rhinitis has been observed[1, 2], although other studies could not confirm this finding.[3, 4] It has been suggested that the beneficial influence of intranasal steroid on the lower airway is due to a restoration of the nasal function leading to an improvement of air conditioning (i.e. filtering, warming and humidifying the air).[5] Other putative mechanisms are a reduction of aspiration of post nasal-secretions, an alleviation of upper-lower airway reflexes or a reduction of reabsorption of mediators or chemotactic factors from the inflammatory process in the nose or sinuses.

Fluticasone propionate (FP) and beclomethasone dipropionate (BDP) are effective steroids against seasonal allergic rhinitis.[6-10] FP possesses twice the anti-inflammatory potency of BDP, as measured by vasoconstrictor assay[6] and is effective as a once daily dosage regimen[10] in half the dose of BDP.[6] The pharmacokinetic properties of FP and BDP are different. The oral bioavailability of intranasal FP is

lower than BDP due to negligible gastro-intestinal absorption[11] and extensive first pass metabolism[12]. This is important for an intranasally administered drug, as a substantial part of the drug (48-78%) is swallowed.[13]
We studied in two consecutive years whether the use of intranasal FP or BDP during the grass pollen season could influence BHR, bronchial calibre and airway symptoms in children and young adults with mild asthma and seasonal allergic rhinitis.

4.3 Materials and methods

4.3.1 Study design

Both studies were placebo-controlled and randomisation double-blind. Treatment was started in the month May in two consecutive pollen seasons, when pollen counts were expected to start rising within two weeks (fig. 1). A forecast on the beginning of the pollen season was given from the University Hospital in Leiden. In the Netherlands the grass pollen season may start anywhere between the beginning of May and half of June, and may last up to 3 months

4.3.2 Study and rescue medication

In the first season (1994) patients received either 200 μg FP aqueous spray or placebo aqueous spray. Patients were carefully instructed to use two actuations of FP or placebo aqueous spray containing 50 μg per actuation in each nostril once daily for six weeks. Patients used the nasal spray in the morning after awakening.
In the second season (1995) there were three study groups. Patients received 200 μg FP aqueous spray, 400 μg BDP aqueous spray or placebo aqueous spray. Patients in the FP group received FP aqueous morning spray and placebo evening spray. Patients in the BDP group received BDP aqueous spray as both morning and evening spray. Patients in the placebo group received two bottles of placebo aqueous spray. The FP and BDP aqueous sprays both contained 50 μg per actuation. All patients were instructed to use two actuations in each nostril twice daily for a period of six weeks. The treatments were dispensed by the manufacturer and were not distinguishable from each other. Patients were instructed to use the nasal spray in the morning after awakening and in the evening before bedtime. Patients were instructed to inspire to total lung capacity before spraying their nasal study medication as a safeguard against aerosol delivery into the lower airways. Concurrent medication (including intranasal vasoconstrictors and oral and/or topical antihistamines) was not allowed during the study except for salbutamol 200 μg rotadisks for asthmatic symptoms and levocabastine eye drops for symptoms of allergic conjunctivitis. Both salbutamol and levocabastine were taken as needed.

4.3.3 Subjects

In the first season 25 patients and in the second season 72 patients aged 8 to 28 years were included in the study. All patients had a clinical history of hay fever and a mild asthma according to ATS criteria[14] with worsening of asthma symptoms in the summer months. All patients had a positive IgE RAST (> 0.7 kU/l, Pharmacia CAP System RAST FEIA) for grass pollen or a positive skin prick test (wheal

diameter > 0.4 wheal diameter of the histamine control) on an aqueous grass pollen extract of 10.000 BU/ml (Vivodiagnost ALK Benelux). Birch pollen and house dust mite allergies were assessed as well. Patients with a birch pollen and/or house dust mite allergy were not excluded from the study. None of the patients had used inhaled, intranasal and/or oral steroids in the last three months prior to the study. Patients using theophyllines, anticholinergics, long-acting bronchodilators and cromoglycate for pulmonary or nasal use, or patients receiving allergy immunotherapy were excluded. Each subject was in a clinical steady state and did not report symptoms of upper or lower respiratory tract infection during at least three weeks prior to the study. Patients with nasal and/or lung pathology different from allergic rhinitis and asthma were excluded. The medical ethics committee of the University Hospital Vrije Universiteit approved the study protocol. Patients and/or parents gave informed consent to participate in the study.

Daily diaries

Symptom scores were recorded in the morning to evaluate nighttime symptoms and in the evening to evaluate symptoms during the day. Recorded symptoms were shortness of breath, wheezing, cough and nasal blockage, and each was scored as 0=none, 1=mild, 2=moderate and 3=severe. In the second season patients also recorded sneezing and runny noses. All patients recorded use of salbutamol. The investigator checked this by counting the used blister packs at each hospital visit.

Methacholine challenge

Patients arrived in the hospital having abstained from inhaled bronchodilators for at least 8 hours. Methacholine challenge was performed to measure BHR according to the guidelines of Birnie et al.[15] Before every challenge test 3 reproducible baseline measurements of FEV_1 and FVC were obtained with a Sensor-Medics pulmonet III computerised water spirometer (IBM PS 235X). The best value of the FEV_1 and the FVC was taken. Zapletal reference values were used to calculate the percentage of the predicted value of the FEV_1 (FEV_1 %pred). Aerosol-dispersed methacholine bromide in unbuffered saline was given in saline solution in doubling concentrations (0.15 to 160 mg/ml). The aerosol was generated by a De Vilbiss 646 nebulizer (De Vilbiss Co., Somerset, Pa.) nebulizer, which was operated with 3 ml solution in the nebulizer cup. The nebulizer was attached to a Rosenthal-French dosimeter (Laboratory for Applied Immunology, Fairfax, Va.) driven by air at 137.8 kPa (20 p.s.i.) with a time adjustment of 0.6 sec. Aerosol delivery was performed according to Verberne.[16] To exclude reactions to the diluent, saline solution was inhaled before metacholine in a similar way. FEV_1 was measured in triplicate 3 minutes after saline solution or methacholine inhalation. The interval between consecutive doses was 5 minutes. The next metacholine dose was not given if FEV_1 had fallen below 80% of baseline. PD_{20} was calculated from a log dose-response plot with linear interpolation of data points.

Pollen-count

The study was performed during the grass pollen seasons of 1994 and 1995. Airborne pollen grains were sampled daily by a Burkard® (Richmansworth, U. K.)

volumetric pollen trap at the University Hospital in Leiden. The distance between Amsterdam and Leiden is 25 miles. Grass pollen counts were expressed as the total weekly count of grains per cubic meter air.

Compliance

In the second season we checked compliance. Therefore we weighed 20 morning and evening bottles containing study medication of each treatment group (Mettler PC 4400 Delta Range weighing machine) before they were handed out to the patients. The mean weight delivered per actuation according to the analysis of the manufacturer was 98.2 mg (FP), 103 mg (BDP) and 98.2 mg (placebo). We calculated the mean used actuations per day. All patients were instructed to use 8 actuations per day. Patients taking more than 70 % (5.6 actuations) or less than 130 % (10.4 actuations) of the total prescribed amount of treatment were considered compliant.[17]

Study scheme

The study started with a screening visit, in which clinical history was obtained and physical examination performed. At the screening visit patients were provided with a diary for recording asthma and nasal symptoms. Use and inhalation technique of salbutamol was explained and/or checked. At the second visit (within two weeks of the first) a methacholine challenge test was performed to measure BHR. When all inclusion criteria were met, patients were randomised into a study group. Patients started the treatment period simultaneously, when pollen counts were expected to start rising within two weeks. During visit three (three weeks after the start of the treatment period) FEV_1 was measured and patients received a new supply of study medication. A second methacholine challenge test was performed at visit 4 (six weeks after the start of the treatment period). In the second study study medication and rescue medication were returned to check for compliance at visits 3 and 4.

4.3.4 Statistical analysis

All methacholine PD_{20} values were logarithmically transformed before analysis. In the first season comparison of subject characteristics at baseline between groups were done with Student's test for independent groups with the exception of the analysis of proportion of allergy between groups which was performed by Chi-square testing. The changes in FEV_1 % pred and PD_{20} within treatment allocation groups were analysed with Student's t-test for paired measurements. Between groups changes were analysed with Student's t-test for independent groups. The difference in the proportion of each group that changed more than one doubling dose was analysed with Fisher exact test. Mean morning and evening symptom scores for nasal blockage and asthma were calculated for a period of 16 days in the first 3 weeks of the treatment period and a period of 16 days in the second 3 weeks of the treatment period. We took the middle 16 days instead of the 21 days of each treatment period because most of the patients filled out the first and last days of the diary incompletely. Symptom scores and the use of salbutamol were analysed with MANOVA for repeated measurements. If a score was missing an interpolation was performed to calculate a score.

In the second season ANOVA was used to evaluate baseline characteristics between treatment groups, with the exception of the analysis of proportion of allergy between groups, which was performed by Chi-square testing. The changes in FEV_1 %pred and PD_{20} within treatment allocation groups were analysed with Student's t-test for paired measurements. ANCOVA was used to evaluate treatment efficacy on PD_{20} against placebo with baseline PD_{20} and age as covariant. Age was taken as covariant because the mean age in the BDP group was significantly lower compared to the other groups. ANOVA was used to evaluate treatment efficacy on FEV_1 against placebo. The symptom scores were analysed with MANOVA for repeated measurements. If a score was missing an interpolation was performed to calculate a score. To evaluate compliance the differences between the estimated number of actuations used and the number of actuations prescribed were analysed with the one sample t-test. The difference in compliance between the treatment groups was analysed with Student's t-test for independent groups. In both seasons a p-value of less than 0.05 was considered statistically significant.

4.4 Results

In the first season four of the twenty-five patients dropped out of the study, two out of each study group. One patient dropped out of the placebo group because of uncontrollable symptoms. Three patients because of a non-compliance to adhere to the protocol. Twenty-one patients were enclosed for the final analysis (table 1). Eleven patients were randomised in the FP group. There were significantly more patients in the FP group with a house dust mite allergy. For the other characteristics there were no significant differences.

In the second season five of the 72 patients dropped out. Two from the BDP group and three from the placebo group, all because of a non-compliance to adhere to the protocol. No patients dropped out from the FP group. Subsequently 67 patients were analysed. 25 Patients were randomly assigned to the FP group, 23 patients to the BDP group, and 24 to the placebo group. Subject characteristics at randomisation were not different, except that mean age in the BDP group was on average 3.4 and 2.6 years lower than in the FP and placebo group respectively (p=0.03, table 1).

4.4.1 Pollen counts

Mean weekly pollen counts during the treatment periods in the pollen season in 1994 and 1995 are shown respectively in figure 1 and 3. In the first season grass pollen counts increased during the treatment period. Measurements after the treatment period were for the majority of the patients just after the peak of the pollen season. In the second season grass pollen counts in the initial 3 weeks were at a relatively low level. Thereafter pollen counts increased quite steeply till approximately 1000/m3. Final measurements started at the peak of the pollen season and lasted for 2 weeks.

Figure 1 Combined asthmatic symptoms score in relation to pollen counts during treatment with intranasal fluticasone or placebo in the grass pollen season of 1994

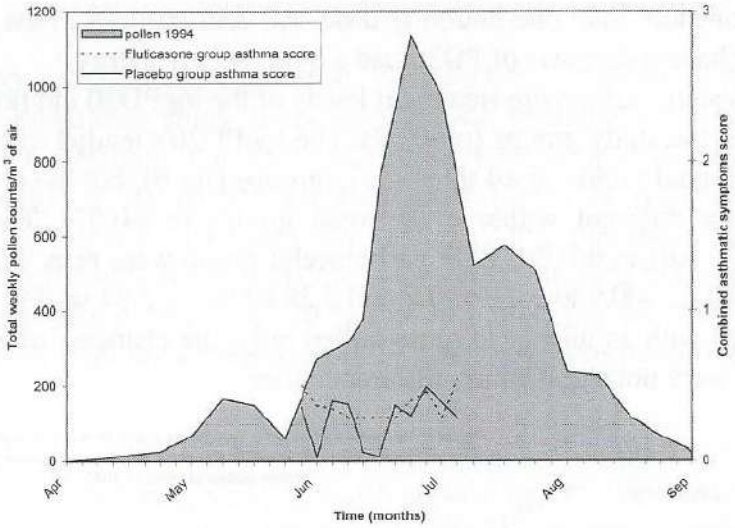
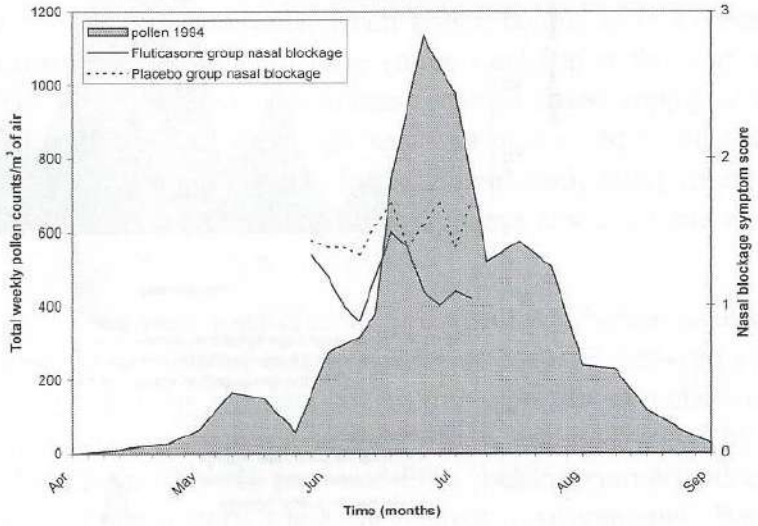


Figure 2 Nasal blockage symptom scores in relation to pollen counts during treatment with intranasal fluticasone or placebo in the pollen season of 1994.



4.4.2 Bronchial hyperresponsiveness

In the first season the pre-trial level of the logPD20 did not differ significantly between groups (p=0.98). The mean logPD20 of the patients decreased significantly both in the fluticasone group (2.43 µg sd 0.8 to 1.86 µg sd 0.85, p= 0.002) and in the placebo group (2.41 µg sd 0.42 to 1.87 sd 0.78, p= 0.01) without any intergroup difference of the change in logPD20 (p=0.2, fig 5). In the FP group all but one patient (10 out of 11 patients) decreased more than one doubling dose, in the placebo

group 6 out of 10 patients decreased more than one doubling dose. This difference in proportion of changing patients between the groups is not significant (p=0.38).
The only patient in the FP group without a birch pollen allergy had a decrease of PD20 of more than one doubling dose. All four patients in the placebo group who did not have a decrease of PD20 had a birch pollen allergy.
In the second season pre-treatment levels of the logPD20 did not differ significantly between the study groups (p =0.52). The logPD20's tended to increase (n.s.) during the treatment period in all three study groups (fig 6), but the changes were not significantly different within or between groups (p =0.97). The changes in mean logPD20 (sd) in the FP, BDP and placebo group were resp. 2.24 sd 0.9 to 2.39 sd 0.8 and 2.02 sd0.9 to 2.23 sd 0.8 and 2.29 sd 0.8 to 2.54 sd 0.9. When patients were analysed with an allergy to grass-pollen only, the changes in logPD20 between the groups were not significantly different either.

Figure 3 Combined asthmatic symptoms score in relation to pollen counts during treatment with intranasal fluticasone, beclomethason or placebo in the grass pollen season of 1995

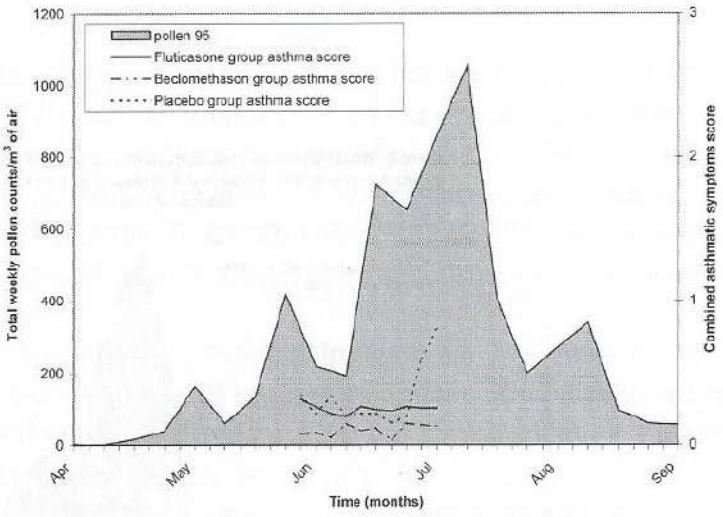
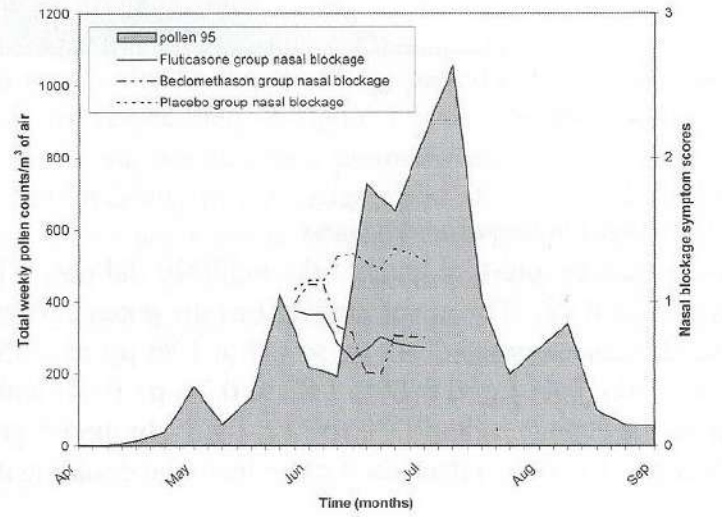


Figure 4 Nasal blockage symptom scores in relation to pollen counts during treatment with intranasal fluticasone, beclomethason or placebo in the grass pollen season of 1995



4.4.3 Bronchial calibre

In the first season the mean FEV1% pred at baseline was not significantly different in the FP and in the placebo group (table 1). The FEV1 % pred did not change during and after the treatment period in the FP group (baseline:109 sd 10, mid-treatment: 110 sd 9.1, end of treatment: 114 sd 10), nor in the placebo group (baseline: 102 sd 15, mid-treatment: 101 sd 16, end of treatment: 102 sd 16).

In the second season the mean FEV1 % pred at baseline was not significantly different in the three groups (table 1). The FEV1% pred increased in all three groups mid-treatment, which was significant in the FP group ($p < 0.001$) and the BDP group ($p < 0.01$), but not in the placebo group (p=0,1). There was no significant difference of the change in FEV1% pred between the groups mid-treatment nor at the end of the treatment (FP baseline: 104 sd 17, mid-treatment: 112 sd 6.0, end of treatment: 103 sd 8.0, BDP baseline: 101 sd 16, mid-treatment: 108 sd 5.1, end of treatment: 103 sd 5.5, Placebo baseline: 100 sd 10, mid-treatment: 103 sd 4.7, end of treatment: 100 sd 5.3).

4.4.4 Symptom scores

In the first season mean daily asthma scores were less than mild (=score 1): the wheezing score was less than 0.5, shortness of breath ranged between 0.5 and 0.8 and cough scores range between 0.5 and 0.8. Mean scores for wheezing, shortness of breath cough, and use of salbutamol did not vary significantly between groups. A score for combined asthma symptoms (wheezing, shortness of breath and cough) is shown in figure 1.

Nasal blockage ranged between mild and moderate (score 1 and 2) and tended to be lower in the FP group, although there was no significant difference between groups over the treatment period (fig 2).

In the second season mean evening scores for wheezing were low (mean score in all three groups less than 0.3) and significantly less in the FP and BDP groups compared to the placebo ($p = 0.024$). Mean day scores for cough, shortness of breath and use of salbutamol did not differ significantly between groups. The scores of nasal blockage and a score for combined asthma symptoms in relation with pollen counts of the second season are shown in figure 3 and 4.

Nasal blockage, sneezing and runny noses in the evening, were significantly less in the FP and BDP groups as compared to the placebo group (p=0.001, p=0.005 and p=0.038 respectively, fig 4).

Figure 5 Change of individual log PD 20 values during the grasspollen season of 1994
– – – : patients without birch pollen allergy

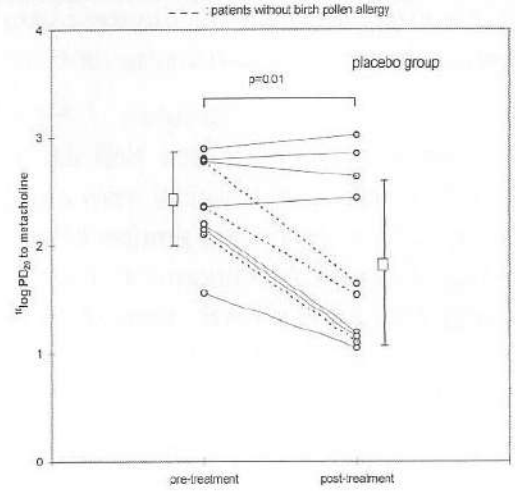
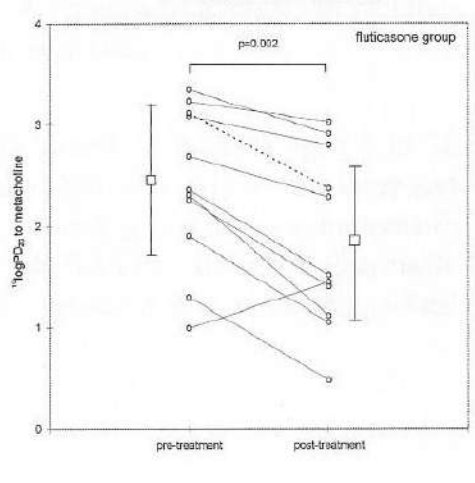


Figure 5 Change of individual logPD$_{20}$ values during the grasspollen season of 1994
– – : only patient without birch pollen allergy



4.4.5 Compliance

All of the patients in the FP group returned their bottles. 3 Patients in the BDP group and 4 patients in the placebo group did not return their medication. The percentage of compliant patients (taking more than 70 % or less than 130 % of the total prescribed amount of treatment) was 62.3%; the number of under-compliant patients was 35.8%. One patient used more than 130% of the prescribed medication. There was no significant difference in compliance between the three treatment groups ($p > 0.1$).

Figure 6 Change of mean $logPD_{20}$ during the grass pollen season of 1995

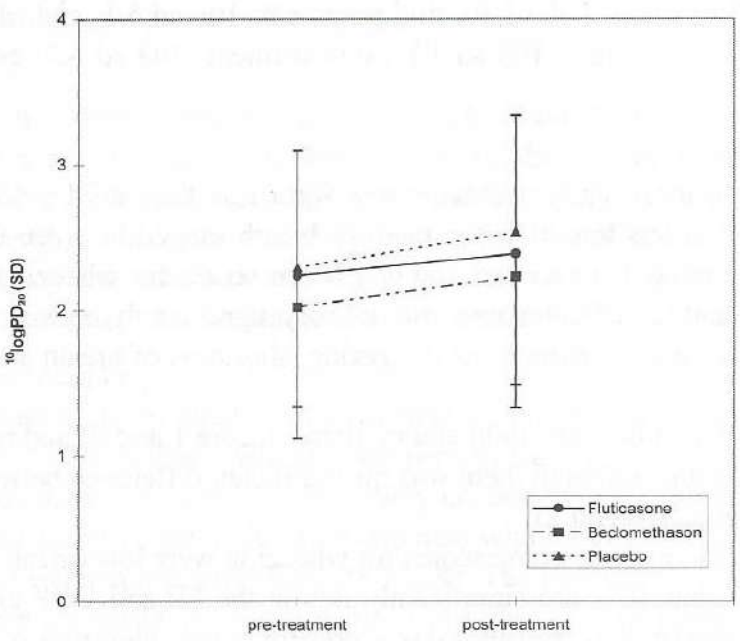


Table 1 Subject characteristics (mean, SD)

	1994			1995			
	Fluti-casone (n =11)	Placebo (n =10)	p-value**	Fluti-casone (n =25)	Beclo-meth. (n =23)	Placebo (n =24)	p-value***
Age (years)	18.4	16.2	Ns	20.5	17.1	19.7	0.03
Sex (f/m)	7/4	6/4	Ns	16/9	14/9	15/9	ns
FEV_1 (% pred)	109(10)	102(15)	Ns	104(17)	101(16)	100(10)	ns
$LogPD_{20}$ (µg)	2.43(0.8)	2.41(0.4)	Ns	2.24 (0.9)	2.02 (0.9)	2.29 (0.8)	ns
Birch pollen*	91%	70%	Ns	64%	57%	42%	ns

Ns : not significant
* : Chi-square testing
** : Student's t-test for independent groups
*** : ANOVA analysis

5

Exercise-induced bronchial obstruction

The Role of the Upper and Lower Airway Mucosa and the impact of physical training

B.J. Thio, H.J. Neijens, J.E. Dankert-Roelse

5.1 Introduction

Exercise-induced bronchial obstruction (EIB) is a transient airway obstruction occurring immediately after and occasionally during exercise. After 4 decades of intensive research an understanding of the underlying mechanisms is gradually being built up, although controversy remains about several aspects of EIB. The aim of this article is to review the pathophysiology of EIB and its implications for treatment options. The focus will be on the role of the mucosa, both in the upper and lower airway, in pathophysiologic mechanisms. The impact of treatment modalities, in particular training programs and inhaled steroids, will also be discussed.

5.2 Clinical aspects

The prevalence of EIB among asthmatics has been found to vary between 40-90% in various published studies.[1-3] EIB is the second most frequent cause of acute airway obstruction in asthmatic patients[4], after viral upper respiratory tract infections. It is not uncommon for EIB to be the first manifestation of asthma and for other symptoms to emerge with time.[1] In adolescence, when asthmatic exacerbations tend to diminish, EIB may persist. In one study 40% of children with documented EIB had no other symptoms of asthma.[5]

A detailed medical history should suggest that a patient suffers from EIB. The most striking aspect of the phenomenon is the short-lived character. The main symptoms of EIB are the same as in an asthma attack e.g. dyspnoea, wheezing, chest tightness and cough. More subtle symptoms such as chest pain (particularly in children and adolescents[6]) or lack of endurance are also reported (Table 1)).

A diagnosis of EIB can be established by objective documentation of airflow obstruction following a standardised exercise challenge. The main factors determining the degree of EIB are the level of ventilation achieved during exercise and the temperature and humidity of inspired air. The strongest stimulus for EIB is running for a period of 6 to 8 minutes in cold, dry air, with medium to high intensity exertion. Values of FEV_1 usually fall to a minimum within the initial 10 minutes after cessation of exercise, with substantial recovery at 30 minutes post-exercise. The response is assessed as the percentage fall in FEV_1 after exercise. The lowest FEV_1 recorded after exercise is subtracted from the pre-exercise value and the difference is expressed as a percentage of the pre-exercise FEV_1. A drop in FEV_1 greater than 10% after exercise is regarded as abnormal and greater than 15% as diagnostic of EIB.[7] If the medical history is not specific, EIB can be differentiated from other conditions by a standardised exercise test (Table 2).

TABLE 1- Symptoms of EIB

Obvious	Subtle
Wheezing	Lack of endurance
Dyspnoea	Chest pain
Cough	Cold air aggravates symptoms
Chest tightness	Symptoms triggered by some sports (running), not by others (swimming)

TABLE 2- Differential diagnosis of EIB6

Poor physical condition
Anxiety/hyperventilation syndrome
Upper airway obstruction/ tracheal syndromes
Spontaneous pneumothorax
Restrictive/other lung disease
Pulmonary embolism
Cardiac disease
Muscle disorders

5.3 Airway physiology and pathophysiology during exercise

The physiological response to exercise in healthy subjects involves cardiovascular, neurohormonal and respiratory changes to meet the increase in the metabolic demands of the muscles.

The physiological adaptations in the respiratory tract during exercise are directed at facilitating high minute ventilation, without the loss of heat and water. An increase in airway calibre is observed at the nasal, tracheal and bronchial levels of the respiratory tract.[8] Nasal ventilation provides heat and water to the inspired air before it enters the lower airways.[9] At the start of vigorous exercise the volume of blood in the capacitance vessels of the erectile tissue in the nasal turbinates decreases and the alae nasi muscles dilate the nares,[10] increasing nasal patency.[8] Nasal resistance decreases further with the intensity but not with the duration of the exercise.[11] The increase in nasal patency is the same in asthmatic and healthy subjects. Due to the increased nasal patency nasal breathing can be maintained during exercise until the upper limit to nasal ventilation alone is reached at a work intensity of approximately 60% of maximal work load.[12] At 90% of maximal workload nasal ventilation contributes only 25-30% to total ventilation.[12] The limitation of nasal breathing alone is due to the increased airway resistance of nasal breathing compared to oral ventilation.[13] Thus with increasing workload gradual switching to mouthbreathing occurs, forcing the lower airways to provide heat and water to condition the incoming air. This results in both evaporative and conductive cooling of the bronchial mucosa.

Although some heat and water are returned to the mucosa on expiration, the net effect is the loss of heat and water from the respiratory tract. It is assumed that this drying and cooling of the lower airways in the presence of airway inflammation elicits EIB. Prevention of these physical changes in the airway mucosa during exercise by compulsory nose breathing abolishes EIB.[14,15]

In both healthy and asthmatic subjects the cross-sectional area of the trachea increases approximately 55% in response to exercise.[13] Vasoconstriction in the sinus network of the tracheal mucosa, comparable to the vascular response in the nasal mucosa, may be responsible for the tracheal enlargement.[16] The increase of trachea and upper airway diameter during exercise is sustained after exercise.[17]

At the bronchial level a mild increase in airway calibre (reflected in a less than 5% improvement of FEV1 over the pre-exercise value) is observed in healthy subjects and stable asthmatics during exercise.[18] Asthmatics show increased expiratory airflow at all lung volumes during exercise. Asthmatics with a high cardiovascular fitness maintain the enhanced expiratory airflow throughout the exercise, while the unfit asthmatics do not.[19] Release of vagal tone and increased levels of catecholamines have been proposed to cause the bronchodilation.[20] However, β2-blockade does not prevent bronchodilation in asthmatics during exercise, although it aggravates the fall in airway calibre after exercise.[21] Furthermore isocapnic hyperventilation without exercise and without an increase in plasma catecholamines will still induce bronchodilation.[22] It has been suggested that the bronchodilation during exercise is largely due to mechanical stretching of the airways.[23] In asthmatics with moderate to severe airflow limitation the lungfunction may improve 25% or more during exercise. The percentage increase in FEV1 or PEFR during exercise was positively correlated with the degree of airflow limitation pre-exercise in a group of asthmatic individuals.[18] During interval exercise a variability in airway tone has been found in asthmatic persons.[24] A reduction in exercise intensity during exercise is followed by a decrease in airway calibre, and an increase in exercise intensity is followed by an increase in airway calibre. The variability in airway tone during variable exercise intensity suggests that as long as the exercise lasts bronchoconstrictor and bronchodilator influences are balanced.

5.4 Changes in the bronchial mucosa during exercise

The precise mechanism of EIB is not yet unravelled. Two hypotheses to explain the phenomenon of EIB in asthmatic subjects are currently popular. The vascular hypothesis is that thermal changes in the lower airway mucosa lead to an increase in local blood flow and increased vascular permeability resulting in airway obstruction.[25] The hyperosmolar hypothesis is based on the assumption that the rapid loss of water from the lower airways leads to an increase in osmolarity of the periciliary fluid.[26, 27] The hyperosmolar state then causes mast cell degranulation with the release of histamine, leukotrienes, prostaglandins, and platelet-activating factor. This will result in smooth muscle contraction and increased bronchial blood flow leading to bronchial obstruction.[18]

5.4.1 Vascular hypothesis

The vascular hypothesis is based on the observation that the rate of rewarming of the airways after exercise influences the magnitude of EIB.[28,29] Inspiring hot humid air after exercise augments EIB, whereas cold air attenuates it.[25] This is the exact opposite of what happens when air of these thermal conditions is inspired during exercise.[30,31] Gradual rather than abrupt termination of exercise reduces the severity of EIB,[32] possibly by reducing the speed and magnitude of rewarming of the airways. The following observations support this hypothesis indirectly.

In the airways of asthmatics the capillary bed is hypertrophied, hyperplastic, and more permeable due to a chronic inflamed state.[33-35] Asthmatic airways rewarmed twice as rapidly as those of normal subjects.[36] Rapid expansion of blood volume with intravenous fluids[35,37] or the application of anti-shock trousers[38] after a hyperventilation challenge amplified the obstructive response in asthmatics, while rapid expansion with intravenous fluids before a hyperventilation challenge blunted the obstructive response.[39,40] An increase in blood volume after hyperventilation probably increases vascular engorgement and mucosal oedema resulting in faster rewarming and slower cooling, while an increase in blood volume before hyperventilation possibly attenuates the cooling of the airways during hyperventilation.[35,37]

Another argument supporting the vascular hypothesis is that various classes of drugs with vasoactive properties can attenuate EIB, presumably by modulating either the cooling phase during exercise or the rewarming phase after exercise or both. Agents with vasodilator activity (α-antagonist,[41] β2-agonists,[42] calcium channel blockers,[43] and cromolyn[44]) might all limit the degree of airway cooling, and through this, minimise the amount of rewarming. In contrast drugs with vasoconstrictor effects (α-agonists[41] and norepineprine[28]) are more likely to achieve their effect by limiting rewarming of the airways.

The vascular hypothesis does not explain all aspects of EIB, particularly the occasional occurrence of during exercise. However Suman et al suggested that this may be due to an increase in body core temperature, which elicits an increase in bronchial blood flow, causing hyperaemia and airway obstruction.[45] In a study into the effect of water loss without heat flux (exercise challenge with hot, dry air) the appearance of EIB was not prevented.[46] Furthermore several investigators have been unable to show that the severity of EIB is influenced by heat loss alone.[30,47]

5.4.2 Hyperosmolar hypothesis

This hypothesis is supported by the observation that mast cell stabilising agents (cromones), histamine receptor antagonists[48] and leukotriene antagonists can prevent EIB.[16,49,50] [16] Furthermore a decrease in humidity of inspired air during exercise and recovery increases the magnitude of EIB.[27,51] In addition, Ingenito et al evaluated bronchoconstrictor responses to cold gas mixtures with a fixed water-carrying capacity but different volume-heat capacities. They found a significant correlation between evaporative heat loss and EIB, but not between total heat loss and EIB.[52] Further support for the hypothesis comes from the fact that hypertonic but not isotonic solutions induce bronchial smooth muscle contraction[15] and vasodilatation of

the tracheal vasculature.[53] Finally hyperosmolar stimuli induce pulmonary mast cell degranulation in vitro.[54] There is, however an equally large body of evidences refuting the hyperosmolar hypothesis. First of all the direct measurement of mediators released into plasma, urine and bronchial lavage fluid in response to exercise show inconsistent results. Furthermore EIB is not entirely prevented under humid climatic conditions. More than half of a group of severe asthmatic subjects had EIB while breathing air conditioned to body temperature and humidity.[27] In addition increasing minute ventilation at constant humidity increases the severity of EIB. McFadden et al studied the effects on lung function of isocapnic hyperventilation challenge with dry frigid air and ambient air. While intrathoracic water loss was largest during the ambient air challenge, the obstructive response was the smallest.[55] He suggested that water fluxes only are important in that they contribute to evaporation leading to airway cooling and rewarming. Gilbert et al have estimated that the changes in surface osmolarity needed to stimulate mast cell degranulation (600-800 mOsm) do not occur in the airways.[35,36] Finally inhaled vasoconstrictive agents, such as methoxamine and norepinephrine, attenuate EIB.[36,56] Vasoconstrictors may reduce the rate of airway rewarming after exercise and prevent vascular engorgement and mucosal oedema. During exercise vasoconstriction in the airway mucosa may increase cooling and drying of the periciliairy fluid, as the rate of substitution of evaporated water is reduced. This should increase the hyperosmolar stimulus. This would, according to the hyperosmolar hypothesis, only tend to aggravate, rather than attenuate, EIB.

In conclusion, although it is generally accepted that EIB is related to fluxes of heat and water in the respiratory tract during exercise-induced hyperpnea, there is no agreement regarding the exact nature of the stimulus that causes EIB. At present there is no direct experimental evidence for either hypothesis. A critical difference between the "osmotic" and the "vascular" theory lies in the state of the bronchial vasculature during exercise. According to the first theory it is dilated and to the other it is constricted. However, the two theories may be combined. Vascular engorgement and oedema will induce the release of inflammatory mediators. This may amplify vascular leakage and induce airway smooth muscle contraction and vascular engorgement. On the other hand inflammatory mediators released in response to mucosal hyperosmolarity affect both the airway smooth muscle and the bronchial microcirculation.

5.5 Cardiovascular fitness and EIB

Understanding the pathophysiology of EIB, both with regard to triggering airway pathophysiology and cardiovascular mechanisms, may help us to find treatment modalities. We have encouraged children to exercise for decades but the question remains whether physical exercise is beneficial against EIB.

Cardiovascular fitness (CVF) is dependent on the oxygen uptake/transport/utilisation chain. In a healthy child ventilation (oxygen uptake) is not a limiting factor. Even at maximal workload less than 70% of the maximal voluntary ventilation is used.[57] The limiting factor for exercise performance is either the ability to

transport oxygen (cardiac output plus haemoglobin level) or the ability to extract and utilise oxygen at the levels of the tissues. However, in children with EIB ventilation often is the limiting factor. This may discourage children from taking part in normal play and sports with peers.[58] Parents, physical educators and teachers may limit children's exercise, worried about provoking asthma.[58] The average CVF of asthmatic children has been observed to be below the mean for healthy children.[59-61] However, when asthmatic children were matched with controls for the degree of physical activity they usually undertook they had a similar CVF.[62-64] Thus the decreased CVF of asthmatic children seems to be due to the reduced physical activity that a substantial number of children with asthma show.

It has been suggested that an increase in CVF can be beneficial in the prevention of EIB.[65] However, a relationship between CVF and EIB was not found,[66] indicating that a normal CVF does not reduce the severity of EIB.[66] Asthmatics with a high CVF have a significantly greater exercise associated increase in airflow reserve during exercise compared to asthmatics with a low CVF, although both groups have a comparable degree of EIB.[19] This may explain the observation that asthmatic children with severe EIB can attain a normal or even high CVF.[66]

Strunk et al demonstrated that a child's psychological adjustment towards asthma correlates better with CVF than does airway calibre, or the occurrence of recent exacerbations.[58] In adult asthmatics Garfinkel et al also found no correlation between CVF and airway calibre, nor did they find a relationship between CVF and AR to metacholine. They were however able to show a significant correlation between activity level and CVF.[68]

In summary, physical inactivity seems to be the cause of a decreased CVF in asthmatic children compared to healthy children. The CVF of asthmatic children appears not to be related to severity of EIB, or airway calibre, but is more closely related to their psychological adjustment towards asthma.

5.6 Effect of physical training on EIB

Numerous studies have shown that physical training can improve CVF of asthmatic children to the same extent as in healthy children.[65,69-72] The question is whether an increase in CVF can influence EIB. If CVF is high, ventilation will be less at a given workload, which decreases the stimulus for EIB. In children with a low CVF a relatively small exercise task leads to high minute ventilation, resulting in a strong stimulus for EIB. Thus a low CVF may be a greater obstacle to normal activities in children with EIB than in healthy children, regardless of the true effect of an increase in CVF on EIB. Several studies have investigated whether physical training could influence the severity of EIB in asthmatics.[69-74 76-78] Most of the studies involved children.[63,67-70] None of the studies was double blind. Only one study was randomised and carefully controlled for medication use (i.e. pre-exercise prophylactics and maintenance treatment). In this study patients in the control group did a light training with no change in CVF.[74] This study was single blind. Unfortunately 40% of the subjects who entered the study dropped out of the study before comple-

tion. The patients in the training group improved their maximal oxygen consumption without an effect on EIB.[74]

Studies assessing the effect of training on EIB can be divided into two groups; the first assessing EIB after training at the same workload as before the physical training (i.e. a lower physiologic stimulus if CVF has increased, Table 3). The second group of studies is those evaluating whether there is a real effect on EIB of an improvement in CVF. In these studies EIB was measured at the same heart rate or percentage of the maximal oxygen uptake as before the training program, offering the same physiologic stimulus for EIB (Table 4). In 7 studies the same workload was used to assess EIB.[65,69,70,73,76-78]. CVF improved in 5 studies.[65,69,70,73,78], in 4 of which a decrease of EIB after a training programme was found.[65,69,73,78] In one study no decrease of EIB was found[70]. Two out of nine patients in this study changed their maintenance medication during the study period, and were found to have increased EIB after the training.

In 6 studies EIB was assessed at the same heart rate before and after training.[71-74,78,79] In all studies an improvement of CVF was found. Of these studies only Haas et al found a reduction in the severity of EIB after training.[73]

In summary, an increase in CVF after physical training in itself does not lead to a significant reduction of EIB. However, a reduction of EIB has been observed in studies, measuring EIB at the same workload before and after training. A decrease in the stimulus for EIB, when CVF has increased, seems to be responsible for this effect. It may be concluded that an increase in CVF can shift the threshold for EIB to a higher workload.[80]

TABLE 3- Effects of physical training on EIB measured with the same absolute workload before and after training.

Reference	Study group	Training	Pre-exercise bronchodilators	CVF	EIB
Henriksen et al 1981[71]	E=28, c=14 9-13 yr	6 weeks running games	+	↑	↓
Arborelius et al 1984[65]	E=30, nc 9-13 yr	3-4 months hf > 170/min	+	↑	↓
Fitch et al 1986[76]	E=10, c=16 9-13 yr	3 months running games	-	0	0
Haas et al 1987[73]	E=37, c=15 Adults	3 months >60-80% hf_{max}	no data	↑	↓
Freeman et al 1989[70]	E=9, c= 6 9-13 yr	5 weeks running training	+	↑	0
Chow et al 1990[77]	E=12, nc 9-14 yr	8 weeks gymnastics/ swimming	+	0	0
Matsumo et al 1999[78]	E=8, c=8 mean age:10 yr	6 weeks swimming	+	↑	↓

E = experimental group
c = control group
nc = no control group
0 = no significant effect
hf = heart frequency during training sessions

TABLE 4- Effects of physical training on EIB measured with the same physiologic stress before and after training.

Reference	Study group	Training	Pre-exercise bronchodilators	CVF	EIB
Nickerson et al 1983 [71]	E=15, nc Mean age: 11 yr	3 months running games	+	↑	0
Fitch et al 1976 [72]	E=46, c=10 9-16 yr	5 months swimming	-	↑	0
Haas et al 1987 [73]	E=37, c=15 Adults	3 months >60-80% hf_{max}	no data	↑	↓
Bungaard et al 1983* [74]	E=16, c= 11 Mean age: 37 yr	2 months interval training	-	↑	0
Veldhoven et al 1999 [79]	E=23, n=24 Mean age 11 yr	Aerobic training 3 months	+	↑	0
Matsumoto I et al 1999 [78]	E=8, c=8 Mean age: 10 yr	Swimming 6 weeks	+	↑	0

E = experimental group
c = control group
nc = no control group
0 = no significant effect
hf = heart frequency during training sessions
* Only study which used randomised groups and control of pre-exercise and maintenance medication.

5.7 The refractory period

Regardless of the exact trigger of EIB, a decrease in upper airway air-conditioning, which occurs during the sudden start of strenuous exercise, is a key factor in the pathophysiology of EIB. If exercise intensity is increased more gradually (warm-up) the appearance of EIB is prevented. The period of time during which a second bout of exercise provokes less than one half of the initial airway response is defined as the refractory period.[81,82] This period can extend up to 4 hours after exercise, although refractoriness to exercise is greatest during the first hours after the initial exercise.[82,83] About half of the patients with EIB show refractoriness to EIB during the first hour after the initial exercise.[84-86] Individuals may display refractoriness to EIB on one occasion but not on another.[87] The presence of a refractory period appears to be independent of the severity of EIB provoked by the first challenge.[88,89]

The mechanism for the phenomenon of refractoriness is unknown. At first it was speculated that a depletion of inflammatory mediators released during the initial exercise caused refractoriness.[82,88] However, levels of inflammatory mediators are inconsistently increased in EIB.[90,91] Another proposed mechanism is that catecholamines released during exercise cause the refractory period by a bronchostabilising effect, but measurements of plasma epinephrine and norepinephrine concentrations in asthmatics show only modest increases on exercise and a rapid clearance of both catecholamines after exercise.[92] A third mechanism proposed comes from the observation that indomethacin, a prostaglandin synthetase inhibitor, blocks refractoriness after exercise. This suggests that refractoriness is dependent on the generation of prostaglandins.[93,94] Exercise induces the generation of vasoactive prostaglandins that may improve the rate of water return to the airways. This effect may well reduce the mucosal drying and/or cooling during exercise,[93] that occur as a result of exercise-induced hyperpnoea. When exercise is repeated, the osmotic/thermal stimulus effects may be diminished, as water is made more readily available by the previous generation of vasoactive prostaglandins.

The induction of refractoriness is not dependent on the prior occurrence of EIB. A warm-up of either low intensity[89] or high intensity[91] before exercise, not inducing EIB, can protect against EIB.[95] The warm-up has to be of sufficient duration to be effective; 3 minutes appearing to be too short.[91] In summary the mechanism of refractoriness is unclear, but maybe at least partially related to the generation of vasoactive prostaglandins enhancing airway blood flow and preventing mucosal drying and cooling. An appropiate warm-up can induce refractoriness to EIB, which can be profitable for patients with EIB.

The suggested involvement of inflammatory mediators in the pathogenesis of EIB raises concerns that EIB may contribute to asthmatic airway inflammation. Observations of recent studies have sustained this concern, since there is an increased prevalence of airway hyperresponsiveness and asthma in cross-country skiers and swimmers compared to healthy control subjects.[96,97] Furthermore clinical pollen allergy is significantly more common in elite athletes than in control subjects.[98] The high prevalence of respiratory symptoms in endurance athletes may be due to the lengthy training with prolonged hyperventilation associated with intense exercise. This leads to repeated and intensive exposure to cold, dry air (skiers), pollen allergen (runners[99]) and chlorine compounds (swimmers[100]), which may very well induce or enhance airway inflammation and AHR, particularly in susceptible subjects. An increase in the maximal airway narrowing to metacholine after the occurrence of EIB has been observed.[101] Furthermore an aggravated reaction to allergen provocation 24 hours after exercise challenge has been found.[10,102] Other studies reported that breathing cold dry air during a histamine challenge test induces increased AHR to histamine in both normal and asthmatic subjects.[104,105] Suzuki found an increased AHR to metacholine shortly after exercise challenge,[106] but this was not confirmed in other studies.[107-109]

5.7.1 *Effect of physical training on airway responsiveness*

A physical training program with repeated exercise challenge may thus potentially increase airway responsiveness in asthmatic patients. Cochrane et al observed no change in airway responsiveness after a training program of 3 months in adult asthmatics, however 9 out of 36 patients changed their maintenance inhalation therapy from cromoglycate to steroids.[110] At the end of the study 30 out of 36 patients used inhaled steroids, whereas only six needed cromoglycate. This change in the maintenance medication may be due to the fact that it became clear during the training programme that protection was not sufficient, or repetitive exercise challenge might have increased their airway responsiveness. Cox et al could not find a change in airway responsiveness to histamine after a rehabilitation program of adult asthmatics, who were on inhaled steroids plus bronchodilators.[111] In the study of Robinson et al there was no change of airway responsiveness to histamine in adult asthmatics after a training program of 12 weeks. Subjects in the control group were non-asthmatic and not training.[112] Finally Schmidt et al observed a decrease in airway responsiveness to histamine in 3 out of 11 children after 6 months training,[113] whereas all nine asthmatic children in the control group showed no change in airway responsiveness. Eight children in that study used maintenance therapy with steroids. In all these studies pre-exercise medication was taken. In daily life pre-exercise medication is often not taken as has been demonstrated in a study of Hussein.[114]

5.7.2 *Airflow induced airway inflammation*

Measurements of inflammatory cells and/or mediators in biological fluids in response to exercise or hyperventilation have provided inconsistent results.[115-127] Bronchoalveolar lavage studies in dogs, guinea pigs[128,129] as well as in humans[127] have suggested that bronchoconstriction induced by airflow is associated with mucosal injury (i.e. shedding of ciliated cells). Morphometric analysis of canine bronchi has confirmed that airflow is able to cause mucosal damage[130,131]. Pre-treatment with β2-agonists protected the canine airway against bronchial obstruction and mucosal injury.[129] Airflow induced bronchial obstruction of canine airways was associated with an influx of neutrophils within 1 hour that tended to diminish after 24 hours.[129] Freed suggested that this neutrophil infiltration may play a role in the rapid mucosal regeneration that occurs simultaneously.[129] Repeated mucosal injury may contribute to a chronically inflamed state of the airways.[129] In only one animal study was airway reactivity measured after airflow induced bronchoconstriction,[133] no increase in airway reactivity occurred after dry air challenge.[133]

In summary repeated exercise does not increase airway responsiveness to pharmacological stimuli when pre-exercise bronchodilators and/or maintenance medication are used. The effect of repeated EIB without pre-exercise bronchodilators and/or maintenance medication on airway responsiveness to pharmacological stimuli is unclear, but may potentially lead to mucosal damage and cell influx, resulting in a modest effect at the highest.

5.8 Effects of corticosteroids on EIB

Although the initial studies assessing the protective effect of prolonged therapy with inhaled corticosteroids against EIB provided inconsistent results,[134-137] studies in the last 25 years have shown a consistent protective effect of inhaled steroids against EIB[138-146] (Table 5). The early studies date back from the seventies when large spacers were not used[135,137] and exercise testing was not standardised, which may explain the lack of efficacy found at that time. The effect of inhaled corticosteroids on EIB is achieved in relatively short period compared to the effect on the airway hyperresponsiveness to pharmacologic stimuli. Two weeks of treatment with inhaled budesonide significantly attenuated EIB.[140] Hofstra et al found a significant reduction in EIB after 3 weeks of fluticasone therapy. There was no further reduction in EIB at regular measurements up to 24 weeks.[139] In contrast prolonged treatment with high doses of inhaled steroids is necessary to obtain a moderate decrease of the airway hyperresponsiveness to histamine.[147] This discrepancy suggests a different mechanism of the effect. The precise mechanisms underlying the effect of corticosteroids on EIB are unknown,[148] but are likely to be related to their anti-inflammatory action on the lower airway wall and particularly on the mucosa. Inhaled steroids inhibit the migration of inflammatory cells to the airways and the release of mediators of inflammation. This results in a decreased inflammatory cell number and activity.[149,150] These immunologic effects may cause the observed protracted decline in airway hyperresponsiveness to histamine, and has been associated with a gradual resolving of airway remodelling. Besides immunologic effects, modern inhaled steroids have potent topical vasoconstrictive and anti-oedematous activity.[151] These vascular effects are likely to occur much faster than the immunologic effects. Since vascular phenomena, such as vascular engorgement and increased vascular permeability leading to mucosal oedema are assumed to be involved, these actions possibly explain the relatively rapid effects on EIB.[1]

Two studies found a dose-related effect of inhaled steroid on EIB.[134,138] Hofstra et al found 200 and 500 μg/day of fluticasone to be equally effective on EIB after 3 weeks.[139] However, the dose reponse curve of fluticasone is rather flat and the dose of 200μg /day Fluticasone is near the optimum dose level.

The time course to generate the effect of corticosteroids on EIB seems to be different between budesonide and fluticasone. The effect of budesonide on EIB had not reached it's maximum after 3 weeks,[140] stabilised after 2 months,[141] whereas the maximum effect of fluticasone was reached within 3 weeks (no earlier observations done).[139] There was no significant correlation between the dose combined with the treatment time and the degree of protection against EIB for budesonide and fluticasone (Figure 1). However, there was a trend of a correlation for budesonide ($r=0.49$, $p=0.13$, $\alpha = 0.05$).

In summary prolonged treatment of inhaled corticosteroid is an effective therapy against EIB. The effect is rapid compared to their effect on airway hyperresponsivenes to pharmacological stimuli. This suggests the relevance of an effect on mucosal microcirculation rather than an immunologic effect.

Legend to Figure 1: Dose response and treatment time effect of inhaled budesonide* and fluticasone on EIB. (* r = 0.49, p = 0.13, $\alpha = 0.05$)

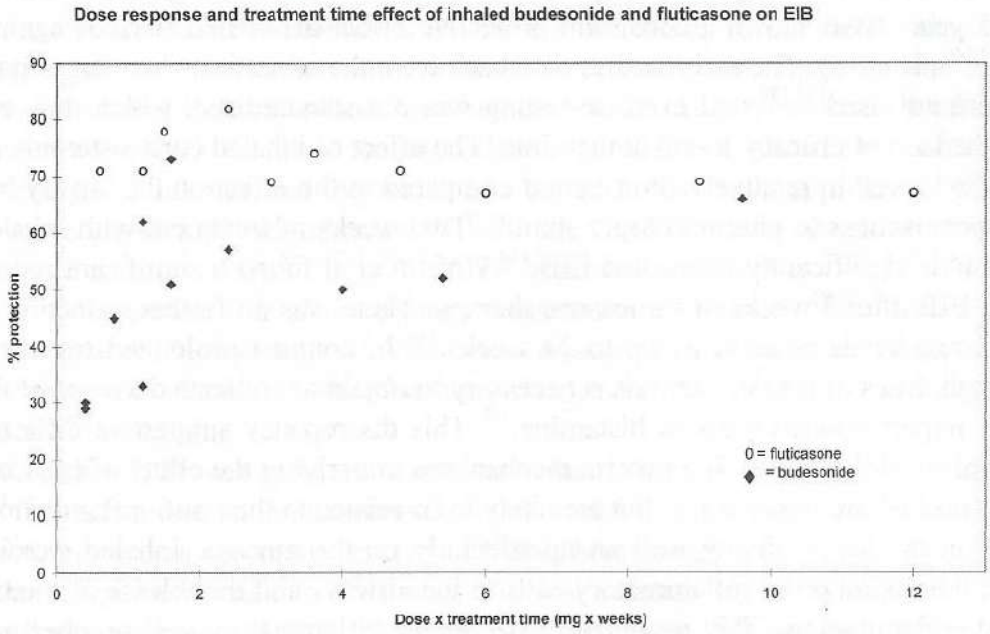


Table 5- Effect of inhaled corticosteroids on EIB

Reference	Drug	Dose µg/day	Duration (weeks)	Test	FEV_1 or PEF	% fall prc/post	% protec-tion**
König et al n=6, children	Beclo-metason	300	1 to 4	Tread-mill	PEF	46.8/33.8	28
Hodgson et al N=10, children	Beta-methason	200-400 600-800	no data	Tread-mill	PEF	No data	No data
Hartley et al N=18, adults	Beta-methason	800	4	Bicycle Ergom.	PEF	24/12	48
Henriksen Et al' 83 n=12 Children*	Bude-sonide	400	1 4	Tread-mill	FEV_1	37/26 18	30 51
Henriksen Et al' 85 n=16 Children	Bude-sonide	400	2	Tread-mill	FEV_1	45/17	62
Venge et al* N=13, adults	Bude-sonide	1000	4	Bicycle	PEF	36/18	50
Waalkens et al N=22, children	Bude-sonide	600	9 36	Tread-mill	PEF	33/16 18	52 45
Vathenen et al N=18, adults	Bude-sonide	1600	6	Tread-mill	FEV_1	27/9	66
Freezer et al N=14 Children	Beclo-metason	400	4 8 12	Bicycle	FEV_1	8/0 0 no data	100 100
Moleman et al N=22 Adults	Bude-sonide	400	3 6	Tread-mill	FEV_1	21/14 9	33 57
Pedersen et al N=19, Children	Bude-sonide	100 200 400	4 4 4	Tread-mill	FEV_1	36/26 36/20 36/10	29 45 73
Hofstra et al N=11, n=14 Children	Fluticasone	200	3 6 12 18 24	Tread-mill	FEV_1	34/10 10 6 9 10	71 71 82 74 71
		500	3 6 12 18 24			36/8 11 12 11 12	78 69 67 69 67

* : no control group

**: $([EIB_{placebo}\text{-}EIB_{active\ drug}]/EIB_{placebo}) \times 100\%$

5.9 Summary

During exercise an increase in nasal patency, an enlargement of tracheal calibre and bronchodilation facilitate a higher airflow both in asthmatic and healthy subjects. After exercise, there is a rapid reversal of lower airway patency in asthmatics, but not in healthy persons, leading to transient bronchial airflow obstruction. In the current pathophysiological concept of EIB a relevant trigger leading to EIB is hyperosmolarity of the periciliar fluid and/or cooling of the airway mucosa. A rapid decrease in nasal breathing, which occurs during the sudden start of strenuous exercise, is an important contributor to these physical changes in the lower airways. A warm-up in conjunction with a an optimal nasal treatment, facilitating a more gradual decrease in nasal breathing, can preserve upper airway air-conditioning longer and prevent the appearance of EIB by induction of a refractory period. Prevention of EIB is a prerequisite for high intensity physical exercise and improvement of CVF. A high CVF in itself this does not reduce the severity of EIB. However, an increase in CVF shifts the threshold for EIB to a higher workload, reducing the degree of EIB at a given workload. Thus an appropiate training programme makes children with EIB less vulnerable for bronchial obstruction in play and sports with their peers.

Besides non-pharmacological treatment modalities pharmacological therapy against EIB is often needed. Pre-exercise bronchodilators will usually produce excellent protection against EIB for about 2 hours. A relatively rapid effect of inhalation of a modern corticosteroid (only a few weeks), is found on EIB compared to a more protracted effect (months to years) on airway hyperresponsiveness. This different speed of efficacy is probably related to the impact of inhaled steroids on the capillairy bed in the airway mucosa. Several other groups of drugs, such as β2-agonists and vasoconstrictors, effecting mucosal microcirculation and taken pre-exercise, can reduce the degree of EIB. This suggests that besides smooth muscle spasm, mucosal features, such as reactive hyperaemia and oedema, contribute substantially to the airway obstruction in EIB. The relative contribution of each in EIB seems to vary from one person to another, indicating the heterogeneity of this phenomenon. Hence, the various effective therapeutic options against EIB, such as inhaled steroids, pre-exercise protection and training programmes, should be tailored to individual patients.

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6

Exercise-induced asthma and cardiovascular fitness in asthmatic children

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6.1 Summary

Background: The role of physical training in the management of children with exercise induced asthma (EIA) is controversial. Aim was to study whether a relationship could be found between the occurrence of EIA and the degree of cardiovascular fitness (CVF) in asthmatic children.

Patients and Methods: Twenty eight children aged 6-13 with mild to moderate asthma, and dyspnoea during or after physical exercise were tested. All patients had a basal FEV1 > 80% predicted. Twelve patients were taking corticocorticosteroid maintenance medication by inhalation and 16 were not. Two exercise tests were performed on a treadmill to assess peak oxygen consumption rate (VO_2max) and the percentage decrease in FEV1 after exercise.

Results: There was no correlation between the VO_2max and the percentage decrease of the FEV1. Patients not taking corticosteroids showed a greater fall of the FEV1 than patients who were taking corticocorticosteroid medication (mean fall FEV1 28.7% v. 6.6%). Four children out of the 12 corticosteroid treated children and two out of the 16 children not taking corticosteroids had a CVF lower than the 5th percentile of healthy dutch children.

Conclusion: A normal cardiovascular fitness does not prevent exercise induced asthma.

6.2 Introduction

Exercise induced asthma is a very frequently encountered symptom in asthmatic children,[1] preventing them to take part in normal play and sports with peers.[2] It has been suggested that normalising CVF is beneficial for the prevention of EIA.[3,4] If so, a relationship between the degree of CVF and the occurrence of EIA may be apparent. Therefore we studied whether such a relationship could be found.

6.3 Methods

6.3.1 Subjects

Thirty one children (19 boys) aged 6-13 years with a mild to moderate asthma took part in the study. All patients had a history of dyspnoea during or after physical exercise leading to problems in play and sports with peers. All patients had a basal FEV1 > 80% predicted on both study days. There had been no exacerbations of asthma for at least three weeks. Two boys and one girl dropped out of the study because they stopped the test before they had reached their maximum exercise level. Of the other children 12 took inhaled corticosteroids; 7 budesonide (daily dosage 800 mg and 400 mg in 3 resp. 4 patients) and 5 beclomethason (daily dosage 400 mg and 200 mg in 4 resp. 1 patient). Five patients took cromoglycate, eleven did not use maintenance medication. All patients took salbutamol as required.

6.3.2 Study design

The children performed two exercise tests: a VO_2max test to assess cardiovascular fitness and an EIA test to assess exercise-induced asthma. All patients did these two

tests on two separate days within two weeks. Temperature and humidity were kept stable during all exercise tests at respectively 18-20 ^{0}C and 40%-45%. Patients were asked not to perform any other exercise on a study day.

VO_2max test

The VO_2max test was performed on a treadmill (Quinton Q45) using a modified Bruce protocol to reduce the steps.[5] The speed and inclination were increased by half the step of the Bruce protocol every 1.5 minutes rather than every 3 minutes. One actuation of a salbutamol 200 mg metered dose pressurized aerosol (Ventolin®) was administered by a large volume spacer (Volumatic®) 15 minutes before each exercise test. The use of salbutamol does not effect VO_2max.[6] Minute ventilation, and mixed expired concentrations of carbon dioxide and oxygen were measured continuously by a verified Mynhardt Oxycon (OX4) to allow calculation of oxygen consumption (VO_2 in l/min), carbon dioxide production (VCO_2 in l/min) and the respiratory quotient (R). Heart rate was measured with a Polar Sport tester®. VO_2max was assumed to be reached, when two of the following criteria were met.[7]

1. Respiratory quotient exceeded 1.0
2. No further increase of heart rate despite increasing load
3. No further increase of oxygen uptake despite increasing load

Exercise induced asthma test

Inhaled bronchodilators were withheld for at least 8 hours before the EIA-test. Before the start of the exercise test on the treadmill the baseline value of the FEV_1 was obtained with a Sensor-Medics pulmonet III computerised water spirometer (IBM PS 235X). The test started with two minutes of running on a treadmill. In these two minutes the inclination of the treadmill was set on 10% and running speed was increased so that the heart rate rose to 180 beats per minute. This speed was maintained for 5 minutes. Children ran with a nose clip. After the exercise had stopped (t =0) we measured FEV_1 at t = 1, 3, 6, 9, 12, 15, 20, 25 and 30 minutes. EIA was calculated as fall of FEV_1 from baseline FEV_1.

$$EIA = \frac{Baseline\ FEV1 - lowest\ postexercise\ FEV1}{Baseline\ FEV1} x\ 100\%$$

6.3.3 Data analysis

We compared the VO_2max of each child with the predicted value for the VO_2max of healthy Dutch children[8] and calculated the % of the predicted VO_2max. The Spearman rank correlation coefficients (r) between % pred VO_2max and % fall of FEV_1 were calculated. Percentage fall of FEV_1 of the corticosteroid treated children versus the non corticosteroid group was compared with a Student's t test.

6.4 Results

In 28 out of 31 children the criteria for a VO_2max were reached. There was no correlation between the % pred. of the VO_2max and the % fall of the FEV_1 in either the

corticosteroid treated children, r =-0.54 (-0.85/ 0.05) or children without corticosteroid treatment, r =0.44 (-0.07/ 0.77) (Figure 1).
The mean (SD) fall in FEV_1 in the corticosteroid treated children was 6.6% (3.1) and in the children without corticosteroid treatment 28.7% (12.5), $p<0.001$. Four out of twelve children in the corticosteroid group and two of the 16 in the non-corticosteroid group had a VO_2max lower than the 5th percentile for their age group (tables 1 and 2).

Table 1 Patient characteristics, %pred VO_2max and percentage fall of FEV_1 in the children without corticosteroid treatment.

	Sex	Age	Med	VO_2max ml/min. kg	percentile group	Pred* VO_2max	% pred VO_2max	% fall FEV_1
1	M	13	-	46.5	p10-25	52.1	89	14
2	F	7	-	42	p25-50	43.8	96	19
3	F	12	-	36	< p5	45	80	14
4	M	11	-	38.3	< p5	51.6	74	41
5	F	10	cromo	41.3	p25-50	44.8	93	40
6	M	8	-	55.6	p75-90	50.2	111	35
7	F	8	-	50.3	p75-90	44.6	113	4
8	M	11	-	56.3	p75-90	51.6	109	37
9	M	8	-	56.7	p90-95	50.2	113	16
10	M	10	cromo	57.4	p75-90	51.4	112	34
11	F	10	-	43.8	p25-50	44.8	98	40
12	F	11	nedocr	56.0	> p95	44.9	125	18
13	M	11	-	44.0	p5-10	51.6	85	34
14	M	11	cromo	50.4	p25-50	51.6	98	34
15	M	11	-	47.8	p10-25	51.6	93	46
16	F	12	cromo	51.8	p90-95	45.0	115	34
Mean		10.2					100.3 sd 14.3	28.7 sd 12.5

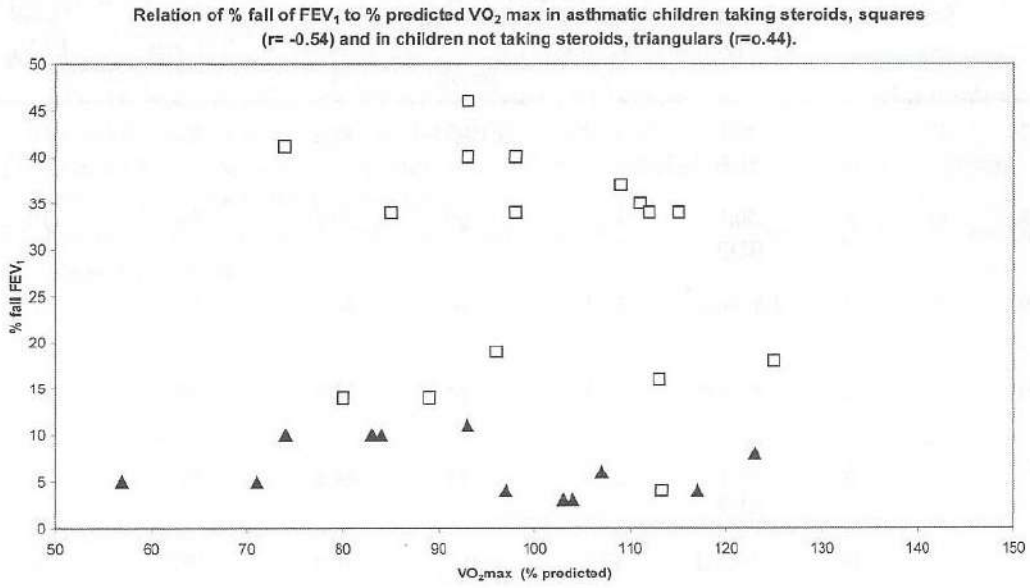
Cromo : Disodium Cromoglycate 5 mg q.i.d.
Nedocr : Nedocromil 2 mg q.i.d.
* Reference 8

Table 2 Patient characteristics, %pred VO_2max and percentage fall of FEV_1 from baseline after exercise in the corticosteroid treated children

	Sex	Age	Dose/ Steroid	VO_2max ml/min.kg	percentile group	pred * VO_2max	% pred VO_2max	% fall FEV_1
17	F	8	400 BDP	37.0	p10-25	44.6	83	10
18	M	8	400 BDP	42.3	< p5	50.2	84	10
19	F	8	400 Bud	31.1	< p5	44.6	71	5
20	M	12	800 Bud	38.5	< p5	51.9	74	10
21	F	8	400 BDP	25.4	< p5	44.6	57	5
22	F	10	400 Bud	47.8	p50-75	44.8	107	6
23	M	10	800 Bud	47.7	p25-50	51.4	93	11
24	M	8	400 BDP	58.5	p90-95	50.2	117	4
25	M	8	400 Bud	51.9	p50-75	50.2	103	3
26	M	8	800 Bud	52.0	p50-75	50.2	104	3
27	M	6	200 BDP	57.4	> p95	46.5	123	8
28	M	7	400 Bud	46.7	p25-50	48.3	97	4
Mean		8.4					111.3 sd 10.1	6.6, sd 3.1

Bud : Budesonide
BDP : Beclomethason dipropionate
* Reference 8

Figure 1:



Discussion

EIA and CVF were not related in both corticosteroid treated patients and patients not taking corticosteroids. This shows that children with severe EIA can attain a normal CVF. Furthermore it indicates that a normal CVF in itself does not prevent severe EIA. Patients without corticosteroid treatment had much more severe EIA than corticosteroid treated patients, which confirms the importance of inhaled corticosteroids in the treatment of EIA.[9] Inhaled corticosteroids reduce the severity of EIA substantially in a relatively short period compared to other indicators of airway responsiveness such as peakflow variability and bronchial responsiveness to metacholine.[10] In the corticosteroid treated children most children showed no substantial EIA. Their symptoms of exercise induced dyspnea were most probably due to a reduced CVF. To keep up with peers they need to make a greater effort, which can explain their symptoms. We conclude that inhaled corticosteroids are first line therapy for severe EIA. Physical training should be reserved for those children in whom a reduced CVF does not normalise while on inhaled corticosteroid treatment.

6.5 References

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7

A warm-up and cool-down effectively protects children with exercise induced bronchoconstricition (EIB) against EIB during a physical training programme

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7.1 Summary

Background- to investigate the feasibility of a training programme aimed at increasing cardiovascular fitness (CVF) in children with exercise induced bronchoconstriction (EIB).
Methods- Six children with EIB participated in a training programme of 6 weeks. Training sessions were three times a week and started with a warm-up and ended with a cool-down to avoid the usage of bronchodilators. Before and after the programme CVF and EIB were assessed.
Results- All children completed the training programme nearly without the appearance of EIB during training sessions and CVF increased significantly.
Conclusion- Physical exercise training preceded by a warm-up and ended with a cool-down, but without pre-exercise bronchodilators, effectively prevents EIB in children with asthma.

7.2 Introduction

Exercise-induced bronchial obstruction (EIB) is highly prevalent in asthmatic children.[1] Pre-exercise bronchodilators offer excellent protection against EIB.[2] However, in daily life most asthmatic children exercise without pre-medication.[3] EIB may lead to a reduced level of cardiovascular fitness (CVF) due to avoidance of exercise or inability to attain a high intensity of exercise.[4] A training programme with carefully controlled pre-exercise bronchodilators to protect against EIB can increase CVF.[5]
Besides the use of pre-exercise bronchodilators a warm-up [6] and a cool-down [7] can protect against EIB. We performed a study in asthmatic children with EIB to assess the feasibility of a physical training programme aimed at improving CVF without the use of pre-exercise bronchodilators.

7.3 Methods

7.3.1 Patients

Six children aged between 7-13 year (five boys and one girl) with mild to moderate asthma entered the study. All children had a history of EIB and a fall in forced expiratory volume (FEV_1) of more than 10% from baseline after an exercise test in a pre-study visit. None of the patients had used steroids in the last three months prior to the study. Two children used maintenance therapy with inhaled cromoglycate. This was maintained during the study.

7.3.2 Study design

Prior to the training programme all children performed three tests: a peak oxygen consumption (VO_2max) test to assess CVF, an exercise test to assess EIB and a metacholine provocation test to assess bronchial responsiveness (BR). All three tests were performed on three separate days within two weeks. Inhaled drugs were withheld for at least 8 hours before the tests. Exercise tests were performed on a treadmill (Quinton Q45) and heart rate was continuously monitored with a radiographic

device (Polar Sport tester). In the first two weeks after the training programme the subjects performed the tests again at the same time of the day as before the training programme. The EIB test was performed at the original external workload.

Training-programme
Three one-hour exercise sessions were conducted weekly for 6 weeks. The sessions had four phases: warm-up, endurance, cool down and fun phase. The warm-up phase was 10 minutes and involved slow jogging. The endurance phase was 10 minutes long during the first week, and was lengthened by 2 minutes per session each week to 20 minutes in the last training week. This phase consisted of running games. The cool-down phase consisted of 5 to 10 minutes of slow walking. A fun phase with recreational games was added to all sessions. The exercise intensity was monitored with a Polar Sport tester. The endurance phase was designed to raise the heart rate > 80% of predicted maximum. Before and after each training session and when indicated during a training session peak expiratory flow rate (PEFR) was measured.

Measurements:
1. Peak oxygen consumption

VO_2max was assessed using a modified Bruce protocol. The speed and inclination were increased by half the step of the Bruce protocol every 1.5 minutes. Salbutamol 200 µg was administered 15 minutes before each VO_2max test to avoid limitation of performance by EIB. Minute ventilation and mixed expired concentrations of carbon dioxide and oxygen were measured continuously by a verified Mynhardt Oxycon (OX4) to allow calculation of oxygen consumption (VO_2 in l/min), carbon dioxide production (VCO_2 in l/min) and the respiratory quotient (R). VO_2max was assumed to be reached when two of the following three criteria were met: respiratory quotient exceeds 1.0, no further increase of heart rate despite increasing load at a value close to the theoretical maximal heart rate (210-age in years), and/or no further increase of oxygen uptake despite increasing of load.

2. Exercise induced bronchial obstruction test

Before the start of the exercise test the baseline value of the FEV_1 was obtained with a Sensor-Medics pulmonet III computerised water spirometer (IBM PS 235X). Temperature and humidity were kept stable during all exercise tests at respectively 18-20^{0}C and 40%-45%. The test started with two minutes of running on a treadmill, during which the inclination of the treadmill was set on 10% and running speed was increased to raise the heart rate to approximately 180 beats per minute. This speed was maintained for 5 minutes. Children ran with a nose clip. After the exercise test we measured FEV_1 during 30 minutes. EIB was calculated as maximal % fall in FEV_1 from baseline FEV_1.

3. Methacholine challenge

Methacholine challenge was performed to measure bronchial responsiveness (BR) according to the guidelines of Birnie et al.[8] PD_{20} was calculated from a log dose-

response plot with linear interpolation of data points. We regarded a PD_{20} lower than 300 μg in agreement with bronchial hyperresponsiveness.

7.3.3 Statistical analysis

Patients who missed more than 30% of the training sessions were to be excluded from the data analysis. The changes from pre- to post training of VO_2 max and change of the heart rate at the EIB test before and after training were analysed with Student's t-test for paired measurements. We compared the VO_2max of each child with the predicted value for the VO_2max of healthy Dutch children and calculated the % of the predicted VO_2max. The mean % of the predicted VO_2max was compared with the mean VO_2max of healthy Dutch children with the one-sample Student t-test before and after training.

7.4 Results

Patient characteristics at the start of the training are presented in Table 1. Patient no.1 did not have EIB anymore at the baseline measurement and did not reach the criteria for the VO_2max test after the training programme. He was excluded from the analysis of VO_2max. Five out of six children had a BHR.

All children tolerated the training programme and the measurements well and completed the entire training programme. The overall compliance to the training sessions was 81,2% (sd 8,3%). None of the patients missed more than 30 % of the training sessions.

The measured PEFR before and after training were not significantly different for the whole group. During training sessions only one child (patient 6) on one occasion had a symptom of EIB (chest tightness) during the cool down phase of the training. Bronchial obstruction was verified with PEFR measurement (fall of PEFR was 15%) and reversed with 200 μg salbutamol. Subject four had a significantly lower PEFR after the training sessions during the training programme. His fall in PEFR after training sessions never exceeded 15% of baseline.

The mean VO_2 max of the patients increased significantly (Table 1). The heart rate during the EIB test after training was significantly lower than in the test before training (resp. 173.8 beats/min sd 5.2 to 192.2 beats/min, sd 3.4, p=0.002, n=6). The mean %pred VO_2max of the children was not different from the predicted VO_2max of Dutch children before and after the training programme (Table 1). The average time during a training session, in which the heart rate exceeded 160 beats per minute was 19 minutes (sd 9 min).

7.5 Discussion

The main objective of the study was to determine whether asthmatic children could undertake a physical training aimed at increasing CVF. The exercise sessions were not routinely pre-medicated, but started with a warm-up and ended with a cool-down to prevent EIB. The exercise sessions, although sufficiently strenuous, did virtually not evoke EIB. The children tolerated and enjoyed the training programme as suggested by the high attendance to the training sessions.

A warm-up produces a refractory period during which patients are protected against EIB during the first hours of exercise and allows cardiovascular adjustment to a more intensive level of exercise. A cool-down prevents the airways of rapidly re-warming post exercise. Asthmatics rewarm their airways post-exercise faster than normal subjects do[9], which has been speculated to cause EIB[10]. The training sessions, although sufficiently strenuous as documented by heart rate, did not evoke EIB in these children with EIB. This finding implies that children with EIB who are stimulated to participate in sports should not only be instructed to use pre-exercise medication to prevent EIB, but also should be informed about the protective influence of a warm-up and cool-down on EIB. After the training programme we observed a significant improvement of CVF. Other factors causing an improvement in CVF can not be completely excluded, as no control group was used, but it is most likely that the training programme caused the improvement in CVF. Previous studies have shown that asthmatic children can increase VO_2max in a training programme with carefully controlled pre-medicated training sessions[4,11,12]. The use of pre-exercise bronchodilators has considered being an absolute prerequisite for the achievement of a training effect[13] as frequent occurrence of EIB during training sessions may have a deleterious effect on exercise intensity. However the effective protection against EIB of a warm-up and cool-down during the training sessions facilitated to attain a sufficient exercise intensity to improve CVF.

In conclusion physical exercise training preceded by a warm-up and ended with a cool-down effectively prevents EIB in children with asthma.

Table 1 Patient characteristics at entry of the study and peak oxygen consumption before and after training with percentage of the predicted peak oxygen consumption for Dutch children.[1]

Patient no.	Sex	Age	FEV_1% pred	Activity** hr ·week^{-1}	PD_{20} µg metach.	EIB % fall FEV_1	VO_2 max^{pre} ml/min/kg	% pred (1) VO_2 max	VO_2max^{post} ml/min/kg	% pred(1) VO_2 max
1	M	7	106	5	15.2	5	53.8	111	#	
2*	F	12	78	4	88.8	34	51.8	115	57.5	127
3	M	11	79	4	298	46	47.8	93	52.2	101
4	M	12	85	5	> 600	34	44.0	85	45.6	88
5*	M	11	89	4	26.7	34	50.4	98	61.0	118
6	M	8	80	2	207.9	11	52.6	105	53.9	107
Mean		10.2	86.2	4	205	27.3	49.3	101.2	54.0##	108.2
SD		2.1	10.6	1.1	222	15.8	3.5	11.3	5.8	15.1

* Maintenance therapy with disodium cromoglycate 5 mg qid.

** organised physical activity

pre VO_2max before training

post VO_2max after training

\# criteria for peak oxygen measurement not reached

$p < 0.05$ when compared to pre-training value

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8

Effects of a single high dose of fluticasone on exercise induced asthma

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8.1 Summary

A single high dose of inhaled corticosteroid (ICS) can increase airway caliber in adult asthmatics and upper airway caliber in children with laryngitis subglottica. We examined whether a single high dose of Fluticasone propionate (FP) could protect against exercise induced bronchial obstruction (EIB) in asthmatic children. Nine children aged 8-16 years with mild to moderate asthma were included. All children had a history of EIB, which was confirmed by an exercise test. None of them was taking ICS maintenance therapy. The children inhaled either a single dose of 1 mg FP or placebo on two separate days within 7-14 days. After inhalation airway caliber (FEV_1) was measured for four hours. Then an exercise challenge was performed on a treadmill to assess EIB (% fall FEV_1). A significant increase in FEV_1 was observed one hour after inhalation of FP compared to placebo. Response to exercise was expressed as maximal % fall in FEV_1 from baseline (% fall) and as Area Under the Curve (AUC) of the 30 min. time response curve. The % fall FEV_1 after exercise and the AUC were significantly reduced when FP was inhaled compared to placebo (% fall respectively 9.7% vs. 19.2%, $p < 0.04$ and AUC resp. 92.0 % ·min vs. 205.7 % ·min, $p= 0.03$). There was considerable individual variability of the reduction in EIB, with five out of nine children having a clinical significant response. We conclude that a single high dose of inhaled FP has an acute protective effect on the bronchial response to exercise in a substantial part of asthmatic children.

8.2 Introduction

Exercise-induced bronchial obstruction (EIB) is defined as an acute, reversible narrowing of the airways during or following physical exercise.[1] EIB is highly prevalent in children and adults with asthma.[1] Factors determining the severity of EIB are the duration and intensity of the exercise, the humidity and temperature of the inhaled air, and the interval since prior exercise.[2] The strongest stimulus giving rise to EIB is exercising for a period of 6 to 8 minutes in cold, dry air, with an exertion of medium to high intensity.[3] Two hypotheses for the pathogenesis of EIB have been proposed. The first one assumes that exercise induced hyperpnea dries the epithelium, leading to hyperosmolarity of the airway surface fluid. This causes the release of histamine and other inflammatory mediators from the mucosal mast cell resulting in bronchial obstruction.[4] The protective effect of mast-cell stabilizing agents and antagonists of mast cell derived mediators against EIB supports this hypothesis.[5-7] The second hypothesis states that exercise-induced hyperventilation results in airway cooling and vasoconstriction. After exercise, when ventilation has normalized, the airways rapidly rewarm leading to vascular engorgement and mucosal edema resulting in bronchial obstruction.[8] It has been shown that the airways of asthmatics rewarm twice as rapidly as those of normal subjects.[9] Furthermore the presence of a hypertrophied, hyperplastic, and more permeable capillary bed in the airways of asthmatics compared to healthy persons is compatible with the second hypothesis.[10-12] We hypothesized that if increased vascularity plays a role in the

pathophysiology of EIB, a single high dose of ICS may have an acute protective effect against EIB due to its vasoconstrictive and anti-edematous properties. Currently used inhaled corticosteroids (ICS) have potent vasoconstrictive and anti-edematous activity [sie,phi]. It has been suggested that this activity accounts for the rapid beneficial effect of a single high dose of ICS in childhood asthma attacks.[13,14] We investigated therefore if a single high dose of inhaled corticosteroid can protect against EIB in children.

8.3 Methods

8.3.1 Subjects

Nine children with mild to moderate asthma according to ATS criteria were studied.[15] Patient characteristics are summarized in Table 1. The following inclusion criteria were fulfilled at a prestudy visit: 1) a decrease of the FEV_1 of more than 15% at a standardized exercise, 2) age between 8 and 16 years, 3) ability to perform reproducible lungfunction tests, i.e. coefficient of the predicted value variation in 3 of 5 consecutive measurements < 5%, 4) an FEV_1 greater than 70% of predicted value (Zapletal reference values [16] were used to calculate the % of the predicted value of the FEV_1), 5) clinically stable period of at least 3 weeks before the study period. None of the patients had used inhaled, intranasal or systemic corticosteroids in the last three months prior to the study. Patients had not used cromoglycates for pulmonary or nasal use in two weeks prior to the study. Patients using theophylline, anticholinergics and long acting bronchodilators were excluded. All patients used inhaled bronchodilators when needed. Most of the children were recruted in the winter or spring, while most study days were in the summer. The medical ethics committee of the University Hospital Vrije Universiteit approved the study protocol. Parents of patients provided written statements of informed consent.

8.3.2 Study design and study scheme

The study was double blind, randomized, cross-over and placebo-controlled. The children visited the hospital on two separate study days with an interval of 7-14 days. During the study days no bronchodilators were allowed. Patients arrived in the hospital in the morning at 9 -10 am having abstained from inhaled bronchodilators for at least 12 hours. After baseline spirometry including inspiratory and expiratory flow volume curves were measured, the study medication was inhaled, either placebo or 1 mg fluticasone propionate (FP), administered as four inhaled actuations of a metered dose inhaler of 250 μg FP in conjunction with a Volumatic (GlaxoWellcome) spacer device. The four puffs were given one by one. After each puff the child had to take five breaths of sufficient magnitude to move the valve of the Volumatic.[21] For the next four hours flow-volume curves and spirometry were measured every hour. Four hours after administration of the study medication an exercise test was performed. Patients were entertained with video movies during the four-hour period prior to the exercise test to prevent them from any other exercise.

Pulmonary function measurements
A Sensor-Medics pulmonet III computerized water-sealed spirometer (IBM PS 235X) was used to measure lung volumes and flow-volume loops. The flow-volume loop was recorded by instructing the subjects to perform a maximal expiratory effort from total lung capacity (TLC) to residual volume and, immediately after that, a maximal inspiratory effort. FVC, FEV_1, maximal mid-expiratory flow (MEF_{50}) and maximal mid-inspiratory flow (MIF_{50}) were calculated from the best curve.

Exercise challenge
Exercise testing for measuring EIB was performed by running on a treadmill (Marquette 2000) using a standardized protocol.[17] During the test, a radiographic device (Polar Sport Tester) continuously monitored heart rate. Dry air, obtained by pressurized medical air and collected in a Douglas bag (contents 150 liter), was inspired during running using a face mask (Hans Rudolph) with an in- and expiratory port, with the nose clipped. The test started with one minute of running at low speed on the treadmill. The incline of the treadmill was set at 10%. When the child was accustomed to the treadmill, the running speed was increased in a way that the heart rate rose to approximately 90% of the predicted maximum (210-age) by the third minute of the test. This speed was maintained for a maximum of three further minutes. After the exercise challenge FEV_1 was measured in duplicate at t = 1, 3, 6, 9, 12, 15, 20, 25 and 30 minutes. The best FEV_1 at each time point was retained for analysis. The pre-exercise FEV_1 (four hours post- drug) was taken as baseline value.

8.3.3 *Statistical analysis*
The severity of EIB was calculated as maximum % fall in FEV_1 from baseline FEV_1 reached within 15 minutes after exercise and as area- under-the-curve (AUC) of the time-response curve. The latter was obtained from plotting the percentage change in FEV_1 from baseline against time (0 -30 min post-exercise).[18] Because the data of % fall were non-Gaussian distributed (positively skewed), logarithmic transformation was applied before using parametric tests.
The within-patient difference of % fall in FEV_1 and of AUC between periods 1 and 2 was compared between the two treatment order groups using the Student's t-test.
Wilcoxon's signed rank test was used to compare the bronchodilator effect of active treatment with placebo.

The recovery time of the bronchial obstructive response after exercise was defined as the duration between the time point at which FEV_1 had reached its maximal %fall from baseline and the time point at which FEV_1 had returned to at least 95% of baseline. If the fall of FEV_1 after exercise was less than 5% the shortest recovery time was taken. The difference of recovery time was analyzed using the Student's t-test for paired measurements.
The protection index, an estimate of the protection afforded by the active treatment over placebo, was expressed as: % protection = $[(EIB_{placebo} - EIB_{active\ drug}) / EIB_{placebo}] \times 100\%$.
P-values < 0.05 were considered statistically significant.

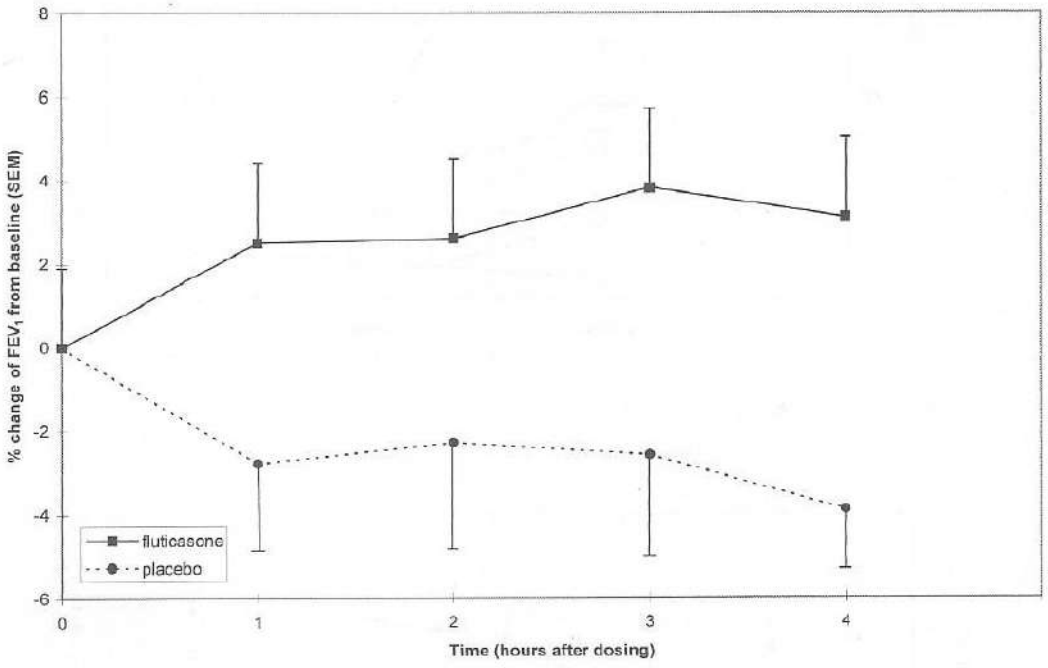
8.4 Results

Nine children entered the study. Mean baseline values of FEV_1 on the two study days did not differ during placebo and active treatment (FEV_1% pred resp. 104 and 102, Table 1).

Effects on bronchus caliber

FP had a slight bronchodilating effect in the first four hours after administration (Figure 1). The maximum mean effect on FEV_1 was reached at 3 hours; the increase from baseline being 3.8 % ± 2.3 % (mean ±SEM). After placebo administration mean FEV_1 decreased with a maximum of 3.9 % ± 1.4 % . Compared with placebo the effect on FEV_1 was just significant at 1 hour and 4 hours after inhalation (α= 0.05), but not at 2 and 3 hours after inhalation.

Figure 1. Bronchodilator action of a single high dose of fluticasone



Effects on EIB

The % fall of FEV_1 was significantly lower when FP was inhaled as compared to placebo (% fall respectively 9.7 %, sd 9.2, vs. 19.2 %, sd 17.3, p =0.038, Table 2, Figure 2). The AUC was significantly less after inhaling FP compared to placebo (AUC resp. 92.0 % ·min, sd 123.6 vs. 208.4 % ·min, sd160.9, p=0.03). Mean % fall in FEV_1 from baseline post-exercise at each time point after inhaling FP or placebo is presented in Figure 3. The protection index was 50 % for % fall of FEV_1 and 56 % for AUC.

Figure 2. Individual results of % fall in FEV_1 after exercise 4 hours after inhaling 1 mg fluticasone

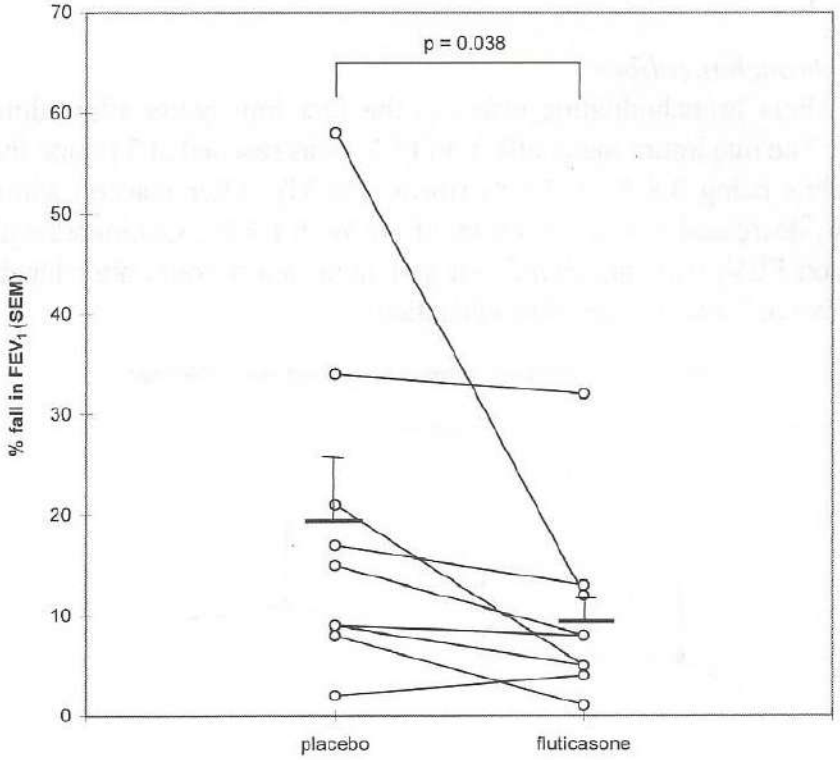
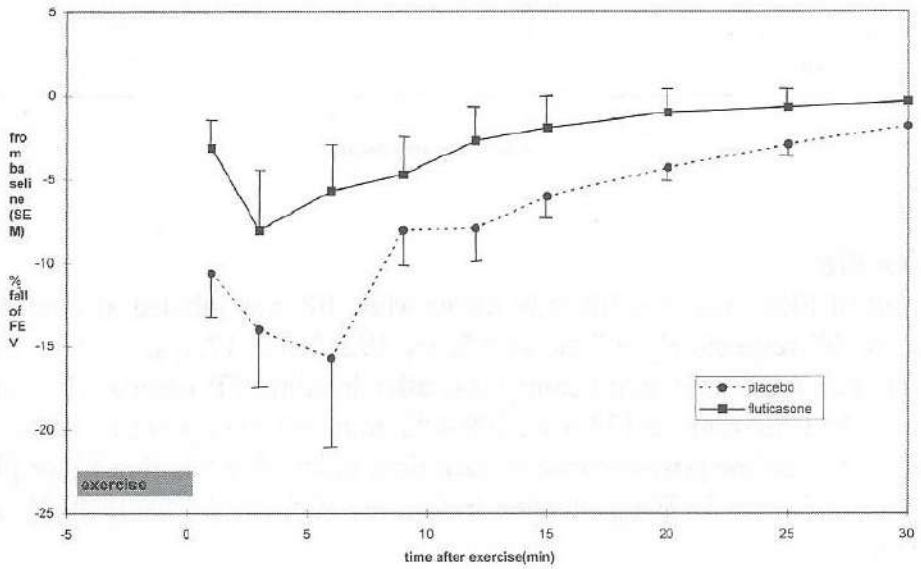


Figure 3 . EIB 4 hours after 1 mg of inhaled fluticasone



Recovery of EIB

30 minutes post exercise all but one patient recovered to greater than 95% of baseline FEV_1 on both study days. In one patient FEV_1 had increased to 94% of the baseline FEV_1 30 minutes post exercise on the FP study day. The mean recovery time of the bronchial obstruction after exercise on the FP study day was significantly shorter than on the placebo study day (resp. 5.6 ±6.5 minutes vs. 13.0 ±8.9 minutes, p=0.036).

8.5 Discussion

We found that a single high dose of inhaled FP halved the degree of EIB 4 hours after dosing in children with mild to moderate asthma.

Three studies have investigated the effect of a single dose of ICS on EIB. All studies measured EIB within 30 minutes after dosing. Two studies used a low dose (200 μg betamethason and 100 μg beclomethason) in astmatic children and observed no prevention of EIB. Venge et al observed a non-significant reduction of EIB after a single inhaled dose of 1 mg budesonide in adult asthmatics.[19] The different results in prior studies compared to our observation may be due to several factors. The dose of the ICS may be an important factor. Recent observations indicate that a higher dose of ICS is required to achieve an early effect than the maintenance dose needed to reduce asthma symptoms in the long run. We studied the effect of 1 mg FP to avoid the risk of missing an acute effect due to underdosing. Prior studies in children used low dose aerosols without large spacers.[20,21] The length of the interval after dosing may have been of influence. The airway dilating effect of a single dose of ICS peaks between 4 and 8 hours.[22-25] Previous studies could therefore have missed an effect measuring EIB too soon. Finally, in previous studies exercise testing was not standardized, and EIB was measured with Peakflow measurements, which is more effort-dependent than FEV_1.

In our study, we measured pulmonary function hourly following inhalation of 1 mg of FP. Even as early as 1 hour after dosing a small but significant increase in airway caliber was apparent. While the changes were small and clinically insignificant, they occurred in children with a mild, stable asthma and a normal baseline FEV_1. In our study group there was little room for improvement and a small increase in FEV_1 may imply a significant effect on airway wall physiology. An acute bronchodilating effect of a single dose of ICS has been observed in several studies in adult asthmatics after inhalation of a single dose of budesonide (100-1600μg).[22-25] Ellul found a dose-response relationship[18] and showed that the bronchodilating property of the ICS was attained by a topical rather than by a systemic effect, as 100 μg inhaled budesonide produced more bronchodilation than 1600 μg oral dose of the drug.[25] The magnitude of bronchodilation achieved after inhalation of a β_2-agonist by a patient did not correlate with the bronchodilation after a single dose of budesonide in the same patient.[24] The combined treatment of a β_2-agonist and a single dose of budesonide produced an additive bronchodilatory effect.[23] This suggests that a single dose of ICS increases airway caliber in a different manner to that of a β_2-agonist, and probably not by smooth muscle relaxation.

We chose to schedule the exercise test 4 hours after dosing. As a result of this schedule we were unable to assess the full course of the effect of a single dose of FP on airway caliber.
We did not compare FP with best current therapy for EIB (β_2-agonist), as we aimed to study the pathophysiology of EIB and not to launch a new therapy for EIB.
We cannot exclude an adverse effect of the placebo aerosol on airway caliber in the first hours after dosing, but we exclude the possibility that the inhalation of the placebo aerosol contributed to the observed difference in EIB, because of the time interval of 4 hours.
Before recruitment into the study the children had shown a fall in FEV_1 of more than 15% during an exercise test. Most of the children had this test in the winter or spring while most study days were in the summer when their asthma had improved. This may be the reason why the mean fall in FEV_1 after exercise on placebo was only 19%. Despite the relatively small margin for improvement of EIB a significant reduction in EIB was observed.
Our sample size was small, based on the observation of Hofstra et al that if a drug is expected to reduce EIB by 50% only five patients are needed in a cross-over design to achieve statistical significance.[18]
The pharmacology of corticosteroids can explain the mechanism of the early effect of a single high dose of ICS on EIB and airway caliber. Corticosteroids upregulate the transcription of anti-inflammatory genes and suppress the transcription of inflammatory genes.[26] This leads to the production of proteins that inhibit the synthesis and release of mediators of inflammation such as prostaglandins, thromboxanes and leucotrienes. The overall effect is the reduction of airway blood flow, plasma exudation, and mucus production and limitation of the migration of inflammatory cells and release mediators of inflammation. In view of these mechanisms it is not surprising that the effects of systemic steroids in asthma require at least 6 to 12 hours to occur.[27]
However, some of the effects of corticosteroids appear faster than can be explained through DNA activation. The synthesis and release of prostaglandins, potent vasodilators and inducers of increased capillairy permeability, from endothelial cells is inhibited within a few minutes.[28,29] A single high dose of ICS may induce vasoconstriction of the hypertrophied and hyperplastic capillary bed of asthmatic airways reducing airway wall thickening. This has the greatest impact in small airways and may account for the increase in airway caliber observed in our study. A rapid effect, starting within 5-10 minutes, of a single high dose of ICS on acute asthma has been observed in pre-school children.[13] An acute reduction of upper airway obstruction in laryngitis subglottica was found as soon as 30 minutes after inhalation of a single high dose of ICS. In animal airways a prompt vascular anti-permeability effect that lasted for several hours was found after a single topical treatment with corticosteroid.[30] The high speed of onset of these effects suggest a non-immunologic phenomenon such as vasoconstriction. Currently used ICS have strong vasoconstrictive and anti-edematous potency compared to the compounds given systemically. FP is approximately 10.000 times more active in this regard than is hydrocortison. In

fact, the acute vasoconstrictive properties of corticosteroids are used to select potent ICS in the skin blanching test.[31] A high dose may amplify such a vascular effect.
It is generally accepted that EIB is related to fluxes of heat and water in the respiratory tract during exercise-induced hyperpnea. There is no agreement regarding the nature of the exact stimulus that causes EIB. There are currently two popular concepts about this mechanism. One states that the rapid loss of water from the lower airways leads to hyperosmolarity of the periciliary fluid.[4] This will induce the release of bronchoconstrictive mediators such as histamine, leukotrienes, prostaglandins, and platelet-activating factor. The other states that thermal changes in the lower airway mucosa lead to an increase in local blood flow and increased vascular permeability.[8] This will result in bronchovascular engorgement and mucosal swelling obstructing lower airways. Regardless of the exact trigger for airway narrowing, the protection of a single inhaled dose of FP against EIB suggests that bronchovascular engorgement and mucosal edema play a substantial role in the pathophysiology of EIB. The variability of the response to FP observed in our study suggests that the relative contribution of vascular engorgement and mucosal edema may vary from person to person, underlining the heterogeneity of EIB in childhood.[32]
We conclude that a single high dose of inhaled steroid offers acute but variable protection against EIB in asthmatic children and speculate the effect is based on a reduction of vascular engorgement and mucosal oedema.

8.6 References

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Table 1-Patient Characteristics

Patient nr.	Age (years)	Sex (F/M)	FEV_1 (%pred.) placebo study day	FEV_1 (%pred.) fluticasone study day
1	16	M	122	124
2	9	F	102	108
3	10	M	85	95
4	11	F	97	95
5	10	M	110	109
6	15	M	100	104
7	11	M	110	82
8	10	F	111	107
9	9	M	103	97
Mean	11.2		104	102
SD	(2.5)		(10.4)	(11.8)

Table 2- % fall of FEV1 from baseline After exercise 4 hours after inhalation of either 1 mg fluticasone or placebo.

patient no.	Placebo	Fluticasone
1	20.8	4.9
2	57.9	11.6
3	7.6	1.0
4	8.7	7.8
5	34.4	32.3
6	16.8	12.8
7	9.4	5.3
8	15.3	7.5
9	1.8	4.0
Mean	19.2	9.7*
SD	(17.3)	(9.2)

* : $p = 0.038$ after logtransformation

9

Summary, general discussion, conclusions, and directions for future research

9.1 Summary

Asthma is characterised by a reversible airway obstruction, on the basis of an inflammatory disorder of the conducting airways of the lungs. The main symptoms of asthma are intermittent episodes of dyspnoea, wheezing, chest tightness and cough. The inflammation is featured by lower airway wall oedema, vascular congestion, smooth muscle contraction and accumulation of mucus in the airway lumen leading to airway obstruction. The inflammatory process is immunologically driven. When the triggers of inflammation, such as allergens and tabacco, are persistent chronic inflammation will ensue. This will lead to a structural remodelling proces of the lower airways, featured by thickening of basement membrane with collagen, smooth muscle hypertrophy and increased vascularity.
The aims of this thesis were to investigate clinical aspects of the relationship between asthma and allergic rhinitis, and to investigate the role of physical exercise in asthmatic children. Particularly, we evaluated the effect of nasal treatment with topical steroid of allergic rhinitis on asthma during the pollen season, the relationship between exercise-induced bronchial obstruction (EIB) and cardiovascular fitness and the effect of a single high dose of inhaled corticosteroid on EIB. Primary outcome parameters of asthma were airway hyperresponsiveness to metacholine, EIB, as measured by fall of FEV_1 after exercise, and airway caliber as measured by FEV_1.

In Chapter 1 a general introduction on the pathophysiology of asthma and allergic rhinitis is given. The mechanism of the action of topical corticosteroids on the allergic inflammation in the upper and lower airway is described and the aims of the studies are presented.

In Chapter 2 the epidemiological relation of asthma and allergic rhinitis is reviewed. It is concluded that the majority of asthmatic children also have allergic rhinitis and that the prevalence of asthma in patients with allergic rhinitis seems to be rising. The putative mechanisms of disease association are reviewed. Furthermore an overview of the treatment of allergic rhinitis is given.

Chapter 3 describes a systematic review of the literature conducted to analyze the effects of intranasal corticosteroids on asthma symptoms. The conclusion of this analysis is that intranasal corticosteroids can reduce asthma symptoms in patients with allergic rhinitis and mild asthma.

In Chapter 4 two clinical studies are reported regarding the effects of intranasal corticosteroids on airway responsiveness and asthmatic symptoms in patients with allergic rhinitis and asthma. The results reported in previous studies are inconsistent. In the first trial we studied the effects of 6 weeks treatment with the intranasal corticosteroid fluticasone, without the use of antihistamines, on airway responsiveness (PD_{20} metacholine), nasal symptoms, asthmatic symptoms, and serum eosinophilic

cationic protein (ECP) levels in 25 children and young adults with asthma and allergic rhinitis. Pollen concentrations slowly rose during the treatment period. The PD_{20} decreased significantly in both the fluticasone group and the placebo group. There was no difference between the change in PD_{20} between the two groups. The fluticasone users reported significantly less shortness of breath and there was a trend towards less nasal symptoms. Serum ECP levels in the placebo group increased; in the fluticasone group serum ECP levels decreased, both changes not being significant. Thus treatment with intranasal steroid could not prevent the increase in airway responsiveness in children and young adults with asthma and hay fever during the pollen season, although respiratory symptoms were less in the fluticasone group.
In the second trial we compared the effect of intranasal fluticasone 200 μg and intranasal beclomethason 400 μg on airway responsiveness and respiratory symptoms. Based on the results of the previous study, we tested the hypothesis that different intranasal steroids in equipotent dose had different effects on airway responsiveness (PD_{20} metacholine). The methodology of this study was similar to the studies performed in the previous year, except for the inclusion of an additional study-arm. Although the pollen concentration increased steadily during the treatment period, there was no change of the PD_{20} metacholine in neither of the three groups. Nasal symptoms were significantly less in the fluticasone and beclomethason group as compared to the placebo group. There was no difference in the effect on nasal symptoms between fluticasone and beclomethason. Mean evening scores for wheezing were also significantly less in both medication groups as compared to the placebo group. FEV_1 improved significantly in the first part under relatively low allergen load in the active treatment groups, but not under placebo, and diminished to baseline value thereafter under high allergen exposure.
Hence, there was no effect of either intranasal fluticasone or intranasal beclomethasone on airway responsiveness, while there was a good and equal effect on nasal symptoms and a temporary increase in airway caliber with both intranasal corticosteroids.

The role of the upper and lower airway mucosa in EIB is reviewed in Chapter 5 and its implications for the treatment of EIB. During exercise an increase in nasal patency, an enlargement of tracheal calibre and bronchodilation facilitate a higher airflow both in asthmatic and healthy subjects. After exercise, there is a rapid reversal of lower airway patency in asthmatics, but not in healthy persons, leading to transient bronchial airflow obstruction. In the current pathophysiological concept of EIB a relevant trigger leading to EIB is hyperosmolarity of the periciliar fluid and/or cooling of the airway mucosa. A rapid decrease in nasal breathing, which occurs during the sudden start of strenuous exercise, is an important contributor to these physical changes in the lower airways. A warm-up in conjunction with an optimal nasal treatment, facilitating a more gradual decrease in nasal breathing, can preserve upper airway air-conditioning longer and prevent the appearance of EIB by induction of a refractory period. Prevention of EIB is a prerequisite for high intensity physical exercise and improvement of cardiovascular fitness. A high cardiovascular

fitness in itself this does not reduce the severity of EIB. However, an increase in cardiovascular fitness shifts the threshold for EIB to a higher workload, reducing the degree of EIB at a given workload. Thus an appropiate training programme makes children with EIB less vulnerable for bronchial obstruction in play and sports with their peers.
Besides non-pharmacological treatment modalities pharmacological therapy against EIB is often needed. Pre-exercise bronchodilators will usually produce excellent protection against EIB for about 2 hours. A relatively rapid effect of inhalation of a modern corticosteroid (only a few weeks), is found on EIB compared to a more protracted effect (months to years) on airway hyperresponsiveness. This rapid protection against EIB is probably related to the impact of inhaled steroids on the capillairy bed of the airway mucosa. Several other groups of drugs, such as β_2-agonists and vasoconstrictors, effecting mucosal microcirculation and inhaled pre-exercise, can reduce the degree of EIB. This suggests that besides smooth muscle spasm, mucosal features, such as reactive hyperaemia and oedema, contribute substantially to the airway obstruction in EIB. The relative contribution of each in EIB seems to vary from one person to another, indicating the heterogeneity of this phenomenon. Hence, the various effective therapeutic options against EIB, such as inhaled steroids, pre-exercise protection and training programmes, should be tailored to individual patients.

In Chapter 6 we examined the relationship between cardiovascular fitness and EIB. It has been suggested that normalising cardiovascular fitness is beneficial for the prevention of EIB. If so, a relationship between the degree of cardiovascular fitness and the severity of EIB may be apparent. Twenty-eight children with asthma and dyspnoea during or after exercise performed two exercise tests on a treadmill. In one test peak oxygen consumption was assessed to measure cardiovascular fitness, and in the other the percentage decrease in FEV_1 after exercise was measured to assess EIB. There was no relationship found between cardiovascular fitness in asthmatic children and EIB. Patients not taking corticosteroids showed a greater fall in FEV_1 than those receiving corticosteroids. We concluded that a normal cardiovascular fitness in asthmatic children does not prevent EIB and that children with severe EIB can attain normal cardiovascular fitness. In addition, we confirmed that inhaled corticosteroids are effective in controlling EIB. Therefore we recommend that physical therapy should be prescribed to those children with EIB in whom a reduced cardiovascular fitness does not normalise while on treatment with inhaled corticosteroids.

Chapter 7 reports a pilot-study investigating whether a training programme of 6 weeks without pre-exercise bronchodilators in children with EIB would be feasible. Cardiovascular fitness, airway responsiveness and EIB were measured before and after 6 weeks of training. Training sessions were three times a week and not premedicated with bronchodilators, which were only given as needed. Each training session started with a warm-up and ended with a cooling down. Peakflow rate was

measured before each training session, and at the occurrence of asthmatic complaints during training sessions. Training intensity was measured by heart rate measurements. There was a good attendance (81%) of the training sessions. All children enjoyed the training sessions and finished the training programme. Only on one occassion EIB was observed, which was verified with PeakFlow measurement. Mean cardiovascular fitness as measured by peak oxygen consumption increased significantly (10%). There was no trend of change of EIB and airway responsiveness after training. Thus children with EIB can participate in a training programme without pre-exercise bronchodilators and exercise symptom-free and even improve their cardiovascular fitness if the exercise is preceded by a good warm-up and followed by a cooling down.

The effect of a single high dose of inhaled corticosteroid (1mg fluticasone propionate) on EIB is described in Chapter 8. We hypothesized that if increased vascularity plays a substantial role in the pathophysiology of EIB, a single high dose of inhaled corticosteroid may have an acute protective effect against EIB due to its vasoconstrictive and anti-edematous properties. To investigate this we selected asthmatic children with EIB, who performed two standardised exercise tests, assessing EIB separated by one week. Four hours before each test either 1mg fluticasone or placebo was inhaled in a double blind manner. The % fall in FEV_1 after exercise was significantly reduced when fluticasone was inhaled as compared to placebo (% fall 9.7% vs. 19.2 % respectively), although the individual response was variable. We speculate that the acute protective effect a single high dose of inhaled corticosteroid (within 4 hours) against EIB is based on a reduction of vascular engorgement and mucosal oedema.

9.2 General discussion

9.2.1 Interactions between allergic rhinitis and asthma

The concurrence of allergic rhinitis in children with asthma is reported to be as high as 80-90%[1,2]. Infiltration of the nasal mucosa with eosinophils can be even present in the absence of symptoms of allergic rhinitis[3]. Since the same genetic defect may be responsible for allergic asthma and allergic rhinitis, the upper and lower airway are lined by the same pseudostratified columnar epithelium, and have the same exposure to inhaled noxes (to a certain extent) the high concurrence of both diseases is not surprising[4]. It has been shown that intranasal corticosteroids have a beneficial effect on symptoms of asthma in patients with mild asthma and allergic rhinitis. In our study intranasal steroids increased airway caliber under low allergen load in patients with mild asthma, whereas we could not confirm an effect on airway responsiveness.

The mechanisms by which the treatment of allergic rhinitis influences asthma are not clear yet. Proposed mechanisms are; improved nasal breathing resulting in a reduced influx of allergic and non-allergic noxes into the lungs, a reduction of post-nasal drip spreading inflammatory mediators in the lungs, an alleviation of neurogenic, and inflammatory reflexes between the upper and lower airway[5], as discussed

in chapter 2. Recently another mechanism was suggested: topical steroids have combined effects on local and systemic targets e.g. the airways and immune cells, circulating or in the bone marrow[6]. Communications between the airways and the bone marrow involving cytokines [7], chemokines[8] and GMCSF[9], potentially promote a pan-airway inflammation, that could be abrogated by systemic pulses of topical corticosteroid absorbed through the airways[6]. Greiff showed that orally inhaled corticosteroids not only prevented the seasonal increase in airway responsiveness in patients with seasonal allergic rhinitis without asthma, but also attenuated the seasonal increase in nasal symptoms and nasal eosinophils[6]. The effects of intranasal corticosteroids on asthma may be achieved by this mechanism. The extra-nasal effects of intranasal corticosteroids and the extra-bronchial effects of inhaled corticosteroids are most likely mild, but can be desirable since the co-existence of both diseases is so frequent. Hence, although intranasal steroids will effect mild asthma to some extent, their role in moderate to severe asthma needs to be established.

9.2.2 Exercise-induced bronchial obstruction

The pharmacological management of EIB in children is straightforward. Pre-exercise bronchodilators give excellent protection and inhaled corticosteroids usually reduce EIB after only a few weeks[10,11]. The pathophysiology of EIB has been a matter of discussion for many years. Two hypotheses for the pathogenesis of EIB have been proposed. The hyperosmolar hypothesis is based on the assumption that the rapid loss of water from the lower airways, due to exercise-induced hyperpnoea, leads to an increase in osmolarity of the periciliary fluid[12]. This hyperosmolar state then causes mast cell degranulation with the release of mediators inducing smooth muscle contraction. The second hypothesis states that exercise-induced hyperpnoea results in airway cooling and vasoconstriction[13]. After exercise, when hyperpnoea suddenly ceases, a rebound hyperaemia follows with rapid rewarming of the airway wall. This may result in engorgement of the capillairy bed and mucosal edema, leading to bronchial obstruction. There is increased vascularity both in terms of number of vessels and area occupied by vessels in the airway wall of asthmatics, potentially increasing the capacity for engorgement. Inhaled corticosteroids currently used are potent vasoconstrictors and can rapidly reduce vasopermeability[14,15]. This property of inhaled steroids has been employed effectively in pediatric upper airway obstruction i.e. laryngitis subglottica[16]. The efficacy of a single high dose of inhaled steroids against EIB, as observed in our study, suggests that bronchovascular engorgement and mucosal edema play a substantial role in the pathophysiology of EIB.

Although there is effective pharmacological treatment against EIB in children, protection for EIB is frequently not achieved in daily life for various reasons[17]. Children are frequently not diagnosed for EIB or not treated properly. The use of pre-exercise bronchodilators before each separate bout of exercise may not be feasible for active school kids. The daily use of inhaled corticosteroid may not be desirable when EIB is the only symptom of asthma. Children with EIB may profit from non-pharmacological methods of protection. A warm-up before exercise and a cool-

down after exercise virtually prevented the appearance of EIB in children with asthma during a training programme of six weeks. A warm-up reduces cooling and drying of the airways during exercise. A cool-down prevents rapidly rewarming of the airways after exercise, which may reduce hyperaemia of the airways. The efficacy of a warm-up and a cool-down against EIB is suggestive of a substantial role of vascular phenomena, such as bronchovascular engorgement and oedema, in EIB.
Effective protection against EIB facilitates regular physical exercise of sufficient intensity to increase cardiovascular fitness. An increase in cardiovascular fitness does not decrease the intrinsic airway responsivenesss to exercise[18,19], but is profitable as it shifts the threshold for EIB to a higher workload. This will reduce the frequency and severity of EIB in asthmatic children during daily play and sports with peers.

9.3 Conclusions

With respect to the effect of intranasal steroid on asthma symptoms, we conclude from the systematic review we performed that in subjects who had both mild asthma and allergic rhinitis, treatment for allergic rhinitis with intranasal steroids produced improvement in asthma symptoms. Omission of treating allergic rhinitis may lead to suboptimal results in asthma treatment. However the effect appears to be insufficient to replace pulmonary therapy.
We found an increase in airway responsiveness in children with asthma and seasonal allergic rhinitis during the first pollen season, as has been observed previously. However, we were unable to confirm the preventive effect of intranasal steroid on the increase in airway responsiveness during the pollen season observed in previous studies. In the consecutive pollen season an increase in airway responsiveness was not observed. This suggests that a certain threshold value of pollination is required to increase airway responsiveness. Neither intranasal fluticasone, nor intranasal beclomethason modified airway responsiveness in children and young adults with seasonal allergic rhinitis and mild asthma during this pollen season. We observed a transient increase in airway caliber in the study groups treated with intranasal corticosteroids under low-grade pollen concentrations. We conclude that a significant effect of intranasal corticosteroids on the lower airways may only be detectable under certain conditions. High pollen concentrations may overwhelm the effect of intranasal corticosteroids on the lower airways; low-grade pollen concentrations may hamper to observe a difference between study and control groups. We did not observe a different effect of intranasal beclomethason or fluticasone on the upper nor on the lower airways, indicating that the inconsistent observation about the effect of intranasal corticosteroids on airway responsiveness is not attributable to different pharmacokinetic properties of these two corticosteroids. We can not exclude that use of intranasal steroids in higher doses or with longer duration or with the use of additive medication, such as antihistamines, can effect bronchial hyperresponsiveness.
With regard to the role of physical exercise on EIB in children with asthma we found no relationship between the level of cardiovascular fitness and the severity of

EIB. However, a high cardiovascular fitness is profitable as it shifts the threshold for EIB to a higher workload, which can reduce the severity of EIB in asthmatic children during play and sports with peers.
We observed that it was possible to increase cardiovascular fitness in asthmatic children with a training programme without the use of pre-exercise bronchodilators. A warm-up and cool down proved to be effective tools to prevent EIB. We recommend that children with EIB should not only be pharmacologically treated, but also be informed about the effects of a warm-up and cool down as a method of protection against EIB.
We found a moderate but significant reduction of EIB after a single inhaled high dose of fluticasone (1 mg) and conclude that a single high dose of inhaled corticosteroid can protect against EIB. This is compatible with the hypothesis that bronchial obstruction in EIB is, at least partially, caused by a vascular phenomenon.

9.4 Directions for future research

A link between the upper and lower airway is evident from epidemiologic, pathophysiologic and clinical studies. Nasal therapy can influence asthma symptoms and in some instances influence lower airway physiology. Future research is needed to determine whether nasal therapy can alter the natural history of asthma.

Influencing the nasal condition can modify lower airway physiology, indicating that there is a link between the upper and lower airway. Several mechanisms underlying this interaction have been proposed. Further research is needed to show the clinical significance of the specific influence of an impaired nasal function, post-nasal secretions and inflammatory reflexes on asthma, and investigate the immunologic interaction between the upper and lower airway.

Aim of the treatment of EIB is that children with EIB can enjoy physical exercise without symptoms and are not restricted in their physical activities. This will facilitate them to attain and maintain a normal level of cardiovascular fitness. On average asthmatic children are unfit. Normalisation of cardiovascular fitness in conjunction with pharmacological therapy is essential to reduce the severity and frequency of EIB. Physical exercise therapy is indicated if a lack of cardiovascular fitness not normalises during treatment against EIB. A training programme can be used to teach children how to decrease EIB pharmacologically and non-pharmacologically. A warm-up and cool down is another effective tool to prevent EIB. Management of EIB should be individually tailored to exercise behaviour in daily life. It is not known whether children spontaneously resume their physical activity resulting in a normalisation of their cardiovascular fitness after therapy against EIB has been started.

The acute protective effect of a single high dose of inhaled corticosteroid on EIB and the efficacy of a warm-up and a cool-down indicate that mucosal vascular phenomena play a role in the mechanism underlying EIB. There was considerable indi-

vidual variability of the degree of protection against EIB after a single high dose of steroids. Recent studies have shown that older children recover slower from EIB than young children. It is therefore likely that different mechanisms play a role in EIB depending on age. To investigate this the effects of a single dose of inhaled steroids and of other groups of drugs reducing EIB in a specific pharmacological way could be studied in different age groups. The finding of different mechanism dependent on age may have implications for the therapy of EIB.
Maintenance therapy with inhaled steroid is supposed to decrease EIB by reducing the immunologic drive of the airway inflammation. The acute protection of a single high dose of steroid against EIB strongly suggests a non-immunologic mode of action, such as vasoconstriction. One could compare the effect of a single dose of inhaled steroid with the long-term efficacy of inhaled corticosteroid on EIB to study the mechanism by which long-term inhaled steroid reduces EIB.
It is unclear if a cool-down adds to the protective effect of a warm-up on EIB. One could compare the effect of a warm-up alone with the addition of a cool-down on EIB. The mechanism underlying the protective effect of a cool-down may be that a more gradual redistribution of the circulating volume from the muscles after exercise, prevents massive overflow of the bronchial vessels. This may prevent oedema and engorgement of the capillairy bed in the airway wall, leading to airway narrowing. Relating the change of peripheral perfusion (skin temperature) after exercise to the severity of EIB could test this hypothesis.

There is some concern that repeated EIB may aggravate airway inflammation, as there is an increased prevalence of asthma in elite endurance athletes compared to control subjects. This high prevalence may be due to the lengthy training with prolonged hyperventilation these people undergo. This leads to repeated and intensive exposure to cold, dry air (skiers), pollen allergen (runners) and chlorine compounds (swimmers) inducing or enhancimg airway inflammation, particularly in susceptible subjects. However , the underlying mechanism is probably distinctively different from airway inflammation caused by allergic sensitization. Repeated exercise in a training programme does not increase airway responsiveness, when pre-exercise bronchodilators and/or maintenance medication are used. It is not known whether prolonged intense exercise without protection can increase allergic airway inflammation in asthmatic subjects.

9.5 References

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10

Samenvatting, algemene discussie en conclusies

10.1 Samenvatting

Astma wordt gekenmerkt door een reversibele luchtwegvernauwing als gevolg van een specifieke ontsteking van de geleidende luchtwegen in de longen. De belangrijkste symptomen van astma zijn intermitterende periodes van klachten zoals kortademigheid, piepen op de borst, hoesten en benauwdheid. Het ontstekingsproces wordt gekenmerkt door zwelling van de luchtwegwand, constrictie van glad spierweefsel, stuwing van bloed en ophoping van slijm in de luchtwegen, leidend tot luchtwegvernauwing. Als de prikkels, die de ontsteking aansturen via immunologische weg, aanhouden, zal een chronisch en specifiek ontstekingsproces het gevolg zijn. Dit kan geleidelijk resulteren in een verandering van de structuur van de luchtwegen.
De doelstellingen van dit proefschrift zijn om het inzicht te verdiepen in de klinische relatie tussen astma en allergische rhinitis en om de wisselwerking tussen astma en lichamelijke inspanning te bestuderen. In het bijzonder werd het effect van nasale steroïden op astma gedurende het pollenseizoen bestudeerd. Verder werd de relatie tussen inspanningsastma en de cardiovasculaire conditie en het effect van een eenmalige hoge dosis van een geïnhaleerd steroid op inspanningastma bestudeerd. Primaire eindpunten van studie waren bronchiale hyperreactiviteit voor metacholine, inspanningsastma, gemeten als de daling van de FEV_1 na inspanning, en luchtwegkaliber gemeten als de FEV_1.

In hoofdstuk 1 wordt de huidige kennis over de pathofysiologie van astma en allergische rhinitis samengevat. Het mechanisme van de werking van lokale steroïden op de allergische ontsteking in de hoge en lage luchtwegen wordt uitgelegd en de doelstellingen van de studies worden beschreven.

In hoofdstuk 2 wordt een overzicht gegeven van de epidemiologische relatie tussen astma en allergische rhinitis. Geconcludeerd wordt dat de meerderheid van kinderen met astma ook een allergische rhinitis heeft en dat de prevalentie van astma bij patiënten met een allergische rhinitis toeneemt. De mogelijke mechanismen die ten grondslag liggen aan de relatie tussen allergische rhinitis en astma worden besproken en grafische weergegeven. Verder wordt een overzicht gegeven van de behandeling van allergische rhinitis.

Hoofdstuk 3 is een systematisch overzichtsartikel van de literatuur met betrekking tot de effecten van nasale corticosteroïden op astma. De conclusie is dat nasale steroïden symptomen van astma kunnen verminderen. Het effect is alleen aangetoond bij patiënten met allergische rhinitis en een mild astma.

In hoofdstuk 4 worden twee klinische studies gerapporteerd met betrekking tot de effecten van nasale steroïden op de bronchiale hyperreactiviteit en astma symptomen bij patiënten met allergische rhinitis en astma. De resultaten gerapporteerd in eerdere studies zijn niet in overeenstemming met elkaar. In de eerste studie onder-

zochten we de effecten van een behandeling van 6 weken met het intranasaal gegeven steroid fluticasone, zonder het gebruik van antihistaminica. Het effect op de bronchiale hyperreactiviteit (PD_{20} voor metacholine), nasale symptomen, astmatische symptomen, en de serum spiegel van 'eosinophillic cationic protein'(ECP) werd gemeten, in 25 kinderen en jong volwassenen met astma en allergische rhinitis gedurende het graspollen seizoen. De pollen concentratie steeg geleidelijk gedurende de behandelperiode. De PD_{20} waarden namen significant af, in zowel de fluticasone groep als de placebo groep. Er was geen verschil in de verandering van de PD_{20} waarden tussen de twee groepen. De gebruikers van fluticasone rapporteerden significant minder klachten van kortademigheid en er was een trend van minder nasale klachten. Serum spiegels van ECP in de placebo groep namen toe; in de fluticasone groep daalden de serum spiegels van ECP, beide veranderingen waren niet significant. Dus de behandeling met intranasale steroïden kon de toename van de bronchiale hyperreactiviteit in kinderen en jong volwassenen met astma en hooikoorts gedurende het pollen seizoen niet voorkomen, alhoewel de luchtwegklachten minder werden in de fluticasone groep.
In de tweede studie vergeleken we de effecten van intranasale fluticasone (200µg) en intranasal beclomethason (400 µg) op de bronchiale hyperreactiviteit en respiratoire klachten. Uitgaande van de resultaten van de eerdere studie, onderzochten we de hypothese dat verschillende intranasale steroïden in equipotente dosis een verschillend effect hebben op de bronchiale hyperreactiviteit (PD_{20} metacholine). De opzet van de studie was hetzelfde als het voorgaande jaar behalve dat er een extra studie groep werd geincludeerd. De pollen concentraties namen gestadig toe tijdens de behandelperiode. Er was geen verandering van de PD_{20} in alle drie de studie groepen. De nasale klachten waren significant minder in de fluticasone groep en de beclomethason groep vergeleken met de placebo groep. Er was geen verschil in het effect op de nasale klachten tussen fluticasone en beclomethason. De gemiddelde avond scores voor piepen waren ook significant minder in beide steroid groepen vergeleken met placebo. De FEV_1 nam significant toe in de eerste helft van het pollen seizoen onder relatief lage pollen concentraties in de groepen met actieve behandeling, maar niet met placebo. Tijdens hoge graspollen concentraties nam de FEV_1 weer af tot de uitgangswaarde in beide behandelgroepen.
Er was dus geen effect van intranasaal fluticasone en beclomethason op de bronchiale hyperreactiviteit, terwijl er een adequaat en gelijk effect was op de nasale klachten en een tijdelijke toename in luchtweg kaliber met beide intranasale steroïden.

De rol van de mucosa van de hoge en lage luchtwegen en de implicaties hiervan voor de behandeling van inspanningsastma wordt besproken in hoofdstuk 5. Gedurende inspanning vindt een toename plaats van luchtwegkaliber op het niveau van de neus, trachea en bronchioli. Dit maakt een groter ademminuutvolume mogelijk. Na inspanning treedt een snelle maar voorbijgaande vernauwing van de lage luchtwegen op bij astmatici, echter niet bij gezonde personen. Ofschoon het onduidelijk is wat precies de prikkel is die leidt tot inspanningsastma (uitdroging en/of afkoeling

in de luchtwegen), is het wel duidelijk dat een snelle toename van de mondademhaling, optredend bij het starten van zware inspanning, een belangrijke rol hierbij speelt. Een warming-up voor inspanning, maakt een ademhaling door de neus langer mogelijk, zodat de ingeademde lucht beter kan worden verwarmd en bevochtigd voordat deze de longen bereikt. Ook zal een warming-up leiden tot een refractaire periode, waarin geen inspanningsastma kan ontstaan. Bescherming tegen inspanningsastma is nodig om zware lichamelijke inspanning te leveren zodat de conditie kan verbeteren. Hoewel een goede conditie op zichzelf inspanningsastma niet vermindert, kan het de drempel waarboven inspanningsastma optreedt wel verhogen. Dus een trainingsprogramma gericht op conditieverbetering maakt kinderen met astma minder kwetsbaar voor inspanningsastma in de dagelijkse sport en spel activiteiten.
Naast bovengenoemde behandelmethodes is medicamenteuze behandeling van inspanningsastma nodig. Bronchusverwijders geïnhaleerd voor inspanning bieden uitstekende bescherming tegen inspanningsastma gedurende ongeveer twee uur. Een onderhouds behandeling met inhalatiesteroïden vermindert inspanningsastma relatief snel (enkele weken), vergeleken met het veel tragere effect op de bronchiale hyperreactiviteit (maanden tot jaren). Dit relatief snelle effect is mogelijk te wijten aan het vasoconstrictieve en anti-oedemateuze effect van inhalatiesteroïden op het capillaire bed in het luchtwegslijmvlies. Verschillende groepen medicijnen geïnhaleerd voor inspanning, die het capillaire bed in het luchtwegslijmvlies beïnvloeden, kunnen inspanningsastma verminderen. Dit kan erop wijzen dat naast constrictie van glad spierweefsel, zwelling van de mucosa en vaatstuwing in de mucosa een belangrijke bijdrage leveren aan de luchtweg obstructie bij inspanningsastma. De relatieve bijdrage van elk afzonderlijk bij inspanningsastma lijkt individueel te variëren, wijzend op de heterogeniciteit van het fenomeen. De verschillende effectieve behandelingsmodaliteiten die er zijn voor inspanningsastma, zoals inhalatie steroïden, bronchusverwijders en lichamelijke training zouden dus moeten aangepast worden aan de individuele patiënt.

In hoofdstuk 6 onderzochten we de relatie tussen de cardiovasculaire conditie en inspanningsastma. Geopperd is dat de cardiovasculaire conditie van invloed is op de ernst van inspanningsastma. Als dit zo is zou er een relatie tussen de ernst van inspanningsastma en de cardiovasculaire conditie kunnen bestaan. Bij 28 kinderen met astma en benauwdheid bij inspanning werden twee inspanningstesten verricht. In een test werd de maximale zuurstofconsumptie gemeten om de cardiovasculaire conditie te bepalen, en in de andere werd de maximale daling van de FEV_1 na inspanning bepaald om de mate van inspanningsastma vast te stellen. Er was geen relatie tussen de ernst van het inspanningsastma en de cardiovasculaire conditie in astmatische kinderen met inspanningsastma. Kinderen die geen onderhoudsinhalatie steroïden gebruikten hadden een grotere daling van de FEV_1 dan diegene die wel inhalatie steroïden gebruikten. We concludeerden dat een normale cardiovasculaire conditie kinderen met astma niet beschermt tegen inspanningsastma en dat kinderen met ernstig inspanningsastma in staat kunnen zijn om een normale cardiovasculaire

conditie te bereiken. Tevens bevestigden we dat inhalatie steroïden effectief zijn in het verminderen van inspanningsastma. Daarom zouden alleen die kinderen in aanmerking moeten komen voor fysiotherapie bij wie de cardiovasculaire conditie niet normaliseert nadat een behandeling met inhalatie steroïden is gestart.

Hoofdstuk 7 rapporteert een 'pilot-study' die onderzocht of kinderen met inspanningsastma een trainingsprogramma van 6 weken kunnen volbrengen, waarin niet standaard voor de training een bronchusverwijder wordt gegeven. De cardiovasculaire conditie, bronchiale hyperreactiviteit en inspanningsastma werden gemeten voor en na het trainingsprogramma. Er waren drie trainingen per week gegeven en bronchusverwijders werden alleen gegeven bij astmatische klachten. Elke training begon met een warming-up en werd afgesloten met een cooling-down. Piekstroommeting werd verricht voor elke training en wanneer er zich klachten voordeden. De trainingsintensiteit werd gemeten met behulp van hartslagmeters. Er was een goede opkomst bij de trainingen (81%). Alle kinderen vermaakten zich tijdens de trainingen en maakten het trainingsprogramma af. Slechts één keer trad inspanningsastma tijdens de trainingen op, geverifieerd met piekstroommeting. De gemiddelde cardiovasculaire conditie, gemeten met de maximale zuurstofopname capaciteit, nam toe (10%). Er was geen trend van verandering van inspanningsastma en bronchiale hyperreactiviteit na de training. Dus kinderen met inspanningsastma kunnen deelnemen aan een trainingsprogramma zonder standaard gebruik van bronchusverwijders en zich inspannen zonder astmatische klachten als de trainingen worden voorafgegaan door een warming-up en worden afgesloten met een cooling-down.

Het effect van een eenmalig hoog gedoseerd inhalatie steroid (1 mg fluticasone propionaat) op inspanningsastma wordt beschreven in hoofdstuk 8. De hypothese was dat als stuwing van het capillaire bed in het luchtwegslijmvlies en zwelling van het luchtwegslijmvlies een belangrijke rol spelen in de pathofysiologie van inspanningsastma, een eenmalige dosis van een inhalatie steroid het inspanningsastma kan verminderen door de vasoconstrictieve en anti-oedemateuze effecten. Om dit te onderzoeken selecteerden we astmatische kinderen met inspanningsastma, die twee gestandaardiseerde inspanningstesten verrichten met een tussenperiode van een week, om de mate van inspanningsastma vast te stellen. Vier uur voor de inspanningstesten werd dubbel blind ofwel 1 mg fluticasone ofwel placebo geïnhaleerd. De daling van de FEV_1 na inspanning was significant minder als fluticasone werd geïnhaleerd vergeleken met placebo (% daling resp. 9.7% en 19.2 %), alhoewel de individuele respons variabel was. We concludeerden dat een eenmalig hooggedoseerde inhalatiedosis van een steroid een direct beschermend effect kan hebben op inspanningsastma bij kinderen met inspanningsastma. We speculeren dat het effect gebaseerd is op een vermindering van vaatstuwing en slijmvlieszwelling.

10.2 Algemene discussie

10.2.1 Interacties tussen allergische rhinitis en astma

Kinderen met astma hebben zeer vaak (80-90%) tevens een allergische rhinitis. Infiltratie van het neusslijmvlies met eosinofielen kan zelfs voorkomen als er geen klachten zijn van een allergische rhinitis. Aangezien dezelfde genetische afwijking ten grondslag ligt aan zowel allergisch astma als allergische rhinitis en de hogere en lagere luchtwegen bekleed zijn met hetzelfde epitheel, is de veel voorkomende combinatie van beide ziektes voor de hand liggend. Het is aangetoond dat intranasale corticosteroïden een gunstig effect kunnen hebben op klachten van astma, hoewel dit effect waarschijnlijk matig is en alleen is aangetoond bij patiënten met een allergisch rhinitis en mild astma. Er is aangetoond dat intranasale steroïden de bronchiale hyperreactiviteit kunnen verminderen in patiënten met een allergische rhinitis zonder evident astma. De manier waarop de behandeling van een allergische rhinitis astma beïnvloedt is onduidelijk. Mogelijk is dat door een betere neusademhaling minder noxen van allergische en niet allergische aard worden geïnhaleerd. Ook is het mogelijk dat er minder aspiratie van nasale secreties (post-nasal drip) met ontstekings-mediatoren is. Verder bestaat de mogelijkheid dat er een afname is van neurogene en inflammatoire reflexen tussen de hoge en de lage luchtwegen, zoals beschreven in hoofdstuk 2. Recentelijk werd een andere mogelijkheid naar voren gebracht: lokale steroïden zouden een gecombineerd effect hebben op de luchtwegen en immuuncellen, circulerend of in het beenmerg. De luchtwegen en het beenmerg communiceren d.m.v. cytokines, chemokines, en GMCSF. Deze mediatoren zouden een ontsteking van de gehele luchtweg kunnen veroorzaken. De gehele luchtweg zou op deze wijze kunnen worden beïnvloed door impulsen van corticosteroïden, lokaal aangebracht in de luchtwegen. Greif toonde aan dat een oraal geïnhaleerd steroid niet alleen de seizoensgebonden toename van de bronchiale hyperreactiviteit voorkwam, maar ook de seizoensgebonden toename van nasale klachten en nasale eosinofilie verminderde. Deze studie werd verricht bij patiënten met allergische rhinitis en bronchiale hyperreactivitieit zonder evident astma. Het effect van nasale steroïden op astma kan via een zelfde mechanisme tot stand worden gebracht. Het pulmonale effect van intranasale steroïden en het nasale effect van oraal geïnhaleerde steroïden is waarschijnlijk mild, maar kan gewenst zijn aangezien astma en allergische rhinitis zo vaak tegelijkertijd voorkomen. Dus, alhoewel intranasale steroïden mild astma tot op zekere hoogte kunnen beïnvloeden, is hun effect in matig en ernstig astma nog onduidelijk.

10.2.2 Inspanningsastma

De medicamenteuze behandeling van inspanningsastma bij kinderen is duidelijk. Bronchusverwijders geïnhaleerd voor inspanning bieden uitstekende bescherming en onderhoudsbehandeling met inhalatiesteroïden vermindert inspanningsastma gewoonlijk reeds na enkele weken. De pathofysiologie van inspanningsastma is reeds jaren een onderwerp van discussie. De twee belangrijkste hypotheses voor de pathogenese van inspanningsastma zijn de hyperosmolaire hypothese en de vascu-

laire hypothese. De eerste stelt dat hyperventilatie tijdens inspanning leidt tot een verlies van water in de luchtwegen. Dit geeft een toename van de osmolariteit van de periciliaire vloeistof, hetgeen resulteert in uitstoting uit de mestcel van mediatoren die bronchospasme veroorzaken. Een tweede hypothese stelt dat hyperventilatie als gevolg van inspanning leidt tot afkoeling van de luchtwegen en vasoconstrictie van de capillairen in het luchtwegslijmvlies. Na inspanning, als de hyperventilatie plotseling stopt, treedt als reactie een versterkte doorbloeding met een snelle opwarming van de luchtwegen op. Dit zou tot stuwing van bloed en zwelling van de luchtwegwand leiden, resulterend in bronchusobstructie. Er is in de luchtwegwand van zelfs milde astmatici sprake van een toename van het aantal vaten en de ruimte bezet door deze vaten. Dit vergroot de potentiële capaciteit voor stuwing en zwelling van de luchtwegwand. Moderne inhalatiesteroïden hebben een sterke vaatvernauwende werking en een snel remmend effect op de vasculaire permeabiliteit. Van dit snelle effect van corticosteroïden wordt gebruik gemaakt bij de behandeling van acute bovenste luchtwegobstructie zoals pseudocroup. De effectiviteit van een eenmalig hoge dosis van een inhalatiesteroïd op inspanningsastma, zoals gevonden in onze studie, suggereert dat stuwing en zwelling van de luchtwegwand een substantiele bijdrage leveren aan de luchtwegvernauwing bij inspanningsastma.

Ofschoon er een effectieve medicamenteuze behandeling bestaat voor inspanningsastma bij kinderen, wordt bescherming tegen inspanningsastma in het dagelijkse leven vaak niet bereikt om verschillende redenen. Inspanningsastma wordt vaak niet herkend, of niet goed behandeld. Het gebruik van bronchusverwijders voor elke lichamelijke inspanning is wellicht in de praktijk niet haalbaar voor actieve schoolgaande kinderen. Het gebruik van onderhoudsmedicatie met inhalatie-steroïden kan niet gewenst zijn indien inspanningsastma het enige symptoom van astma is. Kinderen met inspanningsastma kunnen baat hebben bij niet-medicamenteuze manieren van bescherming tegen inspanningsastma. En warming-up voor inspanning en een cooling-down na inspanning bood goede bescherming tegen inspanningsastma aan kinderen in een trainingsprogramma van 6 weken. Een warming-up vermindert afkoeling en/of uitdroging van de luchtwegen tijdens inspanning. Een cooling-down vermindert de snelle opwarming van de luchtwegen na inspanning, hetgeen een te grote bloedstroom in de luchtwegen na inspanning kan voorkomen. De effectiviteit van een warming-up en een cooling-down pleit voor een belangrijke bijdrage aan inspanningsastma van vasculaire fenomenen, zoals stuwing en slijmvlieszwelling. Goede maatregelen ter voorkoming van inspanningsastma maken het mogelijk dat kinderen zich regelmatig en intensief kunnen inspannen, zodat zij in staat zijn hun cardiovasculaire conditie te verbeteren. Een toename van de cardiovasculaire conditie vermindert niet de intrinsieke hyperreactiviteit van de luchtwegen voor inspanning, maar inspanningsastma treedt pas op bij een zwaardere inspanning. Hierdoor zal de frequentie en ernst van inspanningsastma verminderen, wat kinderen met inspanningsastma in staat zal stellen te kunnen participeren met leeftijdsgenoten in dagelijkse lichamelijke activiteiten.

10.3 Conclusies

In het systematische overzichtsartikel betreffende het effect van nasale steroïden op astma wordt duidelijk dat de behandeling van een allergische rhinitis met intranasale steroïden astmatische klachten kan verminderen in mild astmatische patiënten. Het niet behandelen van een allergische rhinitis kan leiden tot een suboptimale astma behandeling. Het effect van intranasale steroïden op astma lijkt onvoldoende te zijn om de pulmonale behandeling van astma te verminderen of te vervangen.
Een toename van de bronchiale hyperreactiviteit in kinderen met astma en allergische rhinitis werd geobserveerd in het eerste pollen seizoen. We konden niet bevestigen dat intranasale corticosteroïden de toename van de bronchiale hyperreactiviteit gedurende het pollenseizoen kan voorkomen, zoals werd gevonden in eerdere studies. In het daarop volgende graspollenseizoen werd geen toename van de bronchiale hyperreactiviteit gevonden. Waarschijnlijk is er een kritieke mate van graspollen expositie nodig, waarbij de bronchiale hyperreactiviteit toeneemt. Noch intranasaal fluticasone, noch intranasaal beclomethason was in staat de bronchiale hyperreactiviteit te beïnvloeden in kinderen en jonge volwassenen met allergische rhinitis en mild astma tijdens het laatste graspollen seizoen. Wel was er een tijdelijke toename van luchtwegkaliber bij de patiënten behandeld met intranasale corticosteroïden. Een effect van intranasale corticosteroïden op de lage luchtwegen gedurende het graspollen seizoen kan waarschijnlijk alleen gevonden worden onder bepaalde omstandigheden. Een te hoge graspollen concentratie kan het effect van intranasale steroïden teniet doen, terwijl een lage pollen concentratie het moeilijk maakt een verschillend effect te vinden tussen verum en placebo.
We vonden geen verschillend effect van intranasaal fluticasone en beclomethason op klachten van de hoge en lage luchtwegen. De inconsistente resultaten over het effect van intranasale steroïden op de bronchiale hyperreactiviteit wordt dus niet veroorzaakt door verschillende pharmacokinetische eigenschappen van deze twee corticosteroïden. We kunnen niet uitsluiten dat hoger gedoseerde steroïden, een langere behandelingsduur of een combinatie met andere nasale medicatie, zoals antihistaminica, wel de bronchiale hyperreactiviteit kunnen beïnvloeden.

Er was geen relatie tussen de ernst van inspanningsastma en de cardiovasculaire conditie. Toch is een goede cardiovasculaire conditie voordelig, aangezien het de drempel voor inspanningsastma naar een hogere belasting tilt. Dit kan de ernst en frequentie van inspanningsastma in het dagelijks leven verminderen.
Een trainingsprogramma van 6 weken was uitvoerbaar bij kinderen met inspanningsastma zonder het standaardgebruik van bronchusverwijders voor inspanning. Een warming-up en een cooling-down boden goede protectie tegen inspanningsastma en maakten een goede trainingsintensiteit en verbetering van de cardiovasculaire conditie mogelijk. Voor de behandeling van patiënten met astma is het belangrijk om naast medicamenteuze therapie te starten ook patiënten te informeren over het beschermend effect van een warming-up en cooling-down op inspanningsastma.

Het feit dat een eenmalige dosis van een geïnhaleerd steroid bescherming biedt tegen inspanningsastma, pleit voor een belangrijke bijdrage van vasculaire fenomenen in de pathofysiologie van inspanningsastma.

List of abbreviations:

AHR	Airway hyperresponsiveness
BDP	Beclomethasone dipropionate
BHR	Bronchial hyperresponsiveness
BR	Bronchial responsiveness
Bud	Budesonide
CVF	Cardiovascular fitness
ECP	Eosinophilic cationic protein
EIB	Exercise-induced bronchial obstruction · ·
FEV_1	Forced expired volume in one second
FP	Fluticasone propionate
IgE	Immunoglobuline E
PD_{20}	Provocative dose of methacholine causing a 20% fall in FEV_1
PEFR	Peak expiratory flow rate
PAR	Perennial allergic rhinitis
SAR	Seasonal allergic rhinitis

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Curriculum Vitae

Boony Thio werd geboren op 3 april 1965 te Schiedam. In 1983 behaalde hij het Gymnasium Beta diploma aan het Sint Stanislas College te Delft. Na een jaar pharmacie gestudeerd te hebben aan de Rijksuniversiteit te Leiden, begon hij in 1984 aan de studie geneeskunde in Amsterdam aan de Vrije Universiteit. Hij behaalde daar het doctoraal examen in 1988, en vervolgens het artsexamen in 1992. Na zijn arts-examen startte hij zijn werkzaamheden op de afdeling kinderlongziekten van het Academisch Ziekenhuis van de Vrije Universiteit met patient-gebonden onderzoek gecombineerd met poliklinische werkzaamheden. In deze periode werd een start gemaakt met het promotieonderzoek. In 1995 startte hij met de opleiding kindergeneeskunde in het Leids Universitair Medisch Centrum (opleider prof. J.M. Wit). Na afsluiting van zijn opleiding zal hij zich gaan vestigen als kinderarts in het Medisch Spectrum Twente. Hij is getrouwd met Marieke van Schoot en is de trotse vader van drie kinderen Tim-Jan, Mei-An en Anne-Lien.