Exercise induced airway obstruction in children: Patho-physiology and diagnostics

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Chapter 1

General Introduction
Asthma is a common chronic disease in which airway inflammation is associated with airway hyperresponsiveness (AHR) leading to recurrent episodes of wheezing, breathlessness, chest tightness and coughing\(^1\). Worldwide there are approximately 300 million individuals affected with the disease, and the prevalence ranges from 1 to 18% of the population\(^2,3\).

Exercise is a common trigger of AHR and can cause cough, wheezing and chest tightness\(^4,5\). Exercise induced airway obstruction (EIAO) is highly specific for childhood asthma as it reflects asthmatics airway inflammation\(^6,7\) and can be seen as a sign of not well controlled asthma\(^1\).

EIAO occurs in up to 23% of school children\(^7\) and has serious repercussions on the quality of life of these children\(^8\). EIAO reduces the participation in sports and play\(^9\) and 79% of children experience EIAO as the worst component of their asthma\(^10\).

Sports and play are of great importance for a child as it develops both social and motor skills. Symptomatic history is neither a sensitive nor a specific tool to diagnose EIAO\(^11-13\). EIAO may induce a reluctance to exercise and a sedentary lifestyle leading to a low cardiovascular fitness and an increased BMI. A lower cardiovascular fitness leads to a higher ventilation at a relatively low work load which is the trigger for EIAO. Furthermore, a high ventilation causes a feeling of dyspnea which may be misinterpreted by children and their parents as EIAO. An increased BMI has been associated with bronchial hyperresponsiveness for both exercise and metacholine\(^14-16\). In conclusion, asthmatic children with a low cardiovascular fitness and/or a high BMI compared to peers, will encounter a relatively high ventilation during play and sports. Thus increasing the trigger for EIAO and compromising their athletic performance and quality of life (figure 1).

The mechanism through which exercise causes airway obstruction has been the subject of intensive investigation the last decades and is still not fully understood. Most of the studies analyzing the patho-physiology of EIAO have been done in adults, and have shown that airway obstruction occurs after and only occasionally during exercise. Apparently during exercise there is a balance between bronchoconstrictor and bronchodilator influences that

\[\text{Figure 1}, \text{a schematic overview of the interaction between body mass, cardiovascular fitness and EIAO.}\]
prevent EIAO during exercise\textsuperscript{17}. However, after exercise the balance shifts toward bronchoconstriction causing airway narrowing. The two determining factors in EIAO are the level of ventilation and the humidity of the inspired air.

**PATHO-FYSIOLOGY OF EIAO**

There are two theories regarding the patho-physiological basis of EIAO.

The osmotic hypothesis states that the loss of water due to evaporation causes osmotic changes of the epithelium. After the initial insensible loss of water, the airway lining is replenished with water present in the epithelium (figure 2a). The consequential hyperosmolarity is resolved through influx of water, causing a quick fall in osmolarity (figure 2b). This fast reduction in osmolarity of the epithelium is the trigger for mast cells residing in the airway wall to release mediators (figure 2c)\textsuperscript{18}. Kippelen et al. have analyzed the release of mediators through urinary secretion and found that in asthmatic adults prostaglandin E\textsubscript{2} was released after EIAO\textsuperscript{19}. These mediators interact with effector cells and cause airway smooth muscle contraction, mucus hypersecretion and micro vascular leakage\textsuperscript{20,21}. This may happen simultaneously in different parts of the airways.

The vascular hypothesis states that exercise induced hyperventilation leads to evaporation of the airway lining. As a consequence the heat loss of the epithelium causes the vascular bed to constrict during exercise, increasing the patency of the airways. After exercise, as hyperventilation ceases the airways rewarm, and the vascular bed congests and leaks fluids, engorging the epithelium and reducing the patency of the airways\textsuperscript{22}.

**Figure 2a**, after the initial insensible loss of water, the airway lining is replenished with water present in the epithelium.
Hyperventilation during and immediately after exercise causes evaporation of the water of the airway lining. The level of ventilation is determined by the intensity of exercise and a heart rate of 95% of predicted increases the occurrence and severity of EIAO when compared to exercise at a heart rate of 85%\(^2\). The humidity of the inspired air is an important factor of EIAO.

**Figure 2b,** the consequential hyperosmolarity is resolved through influx of water, causing a quick fall in osmolarity.

**Figure 2c,** This fast reduction in osmolarity of the epithelium is the trigger for mast cells residing in the airway wall to release mediators.
as a reduction in the absolute humidity of the inspired air increases both the occurrence and severity\textsuperscript{24}. Although the temperature of the inspired air also seems to effect the EIAO, the occurrence and severity of EIAO does not seem to be influenced by temperature significantly\textsuperscript{24}.

To analyze exercise induced airway obstruction spirometry is routinely used. A drop in the forced expiratory volume in first second (FEV\textsubscript{1}) of 15\% is used as the cut-off for EIAO\textsuperscript{25}, although other cut-offs have been suggested for use in children (13\%)\textsuperscript{26} and research (10\%)\textsuperscript{25}. The use of forced breathing to evaluate EIAO however, may in itself influence the obstruction as deep breathing may lead to bronchodilation\textsuperscript{27} or bronchoconstriction\textsuperscript{28}. The forced oscillation technique (FOT) does not rely on forced breathing maneuvers and is an elegant method to analyze the patency of the airways. The FOT analyzes the resistance and reactance of the airways using acoustical impedance\textsuperscript{29}. The resistive component of respiratory impedance (Rrs) depends on the airway caliber. The reactive component of respiratory impedance (Xrs) incorporates the mass inertive forces of the air column in the conducting airways and the elastic properties of lung periphery\textsuperscript{30} i.e. lung stiffness, intra-parenchymal airway mechanics and airway-parenchyma interdependence.

Exercise alone is a powerful bronchodilator and EIAO characteristically develops after and not during exercise as can be seen in figure 3a. However studies with asthmatic adults have shown that during prolonged submaximal exercise of 30 minutes EIAO can occur during exercise as can be seen in figure 3b, creating a ‘breakthrough’ EIAO\textsuperscript{31-33}. This indicates that the balance between dilating and constricting factors in EIAO can be disturbed during prolonged exercise and that constricting factors can prevail. Children show different dynamics of lung function after exercise than adults. Children develop, sometimes severe, airway obstruction immediately after exercise\textsuperscript{34}, and recover faster than adults, suggesting that EIAO can also occur during exercise in children. In chapter 2 we will analyze the patency of the airways during exercise in asthmatic children by measuring lung function during exercise.

The dynamics of change of the FEV\textsubscript{1} after exercise, corresponding with the patency of the larger, conducting airways\textsuperscript{35} is well known\textsuperscript{31}. Other spirometric indices such as FEF\textsubscript{25} and FEF\textsubscript{75}

**Figure 3a**, The ‘non-breakthrough’ asthmatic airways response to exercise and 3b the ‘breakthrough’ asthmatic airway response to exercise (adopted from Gotshall\textsuperscript{17}).
have been linked with the patency of respectively larger and smaller airways, but have not been used to evaluate the dynamics of EIAO. Although the FOT has been used to evaluate EIAO using change in lower frequency resistance and reactance, the change in time after exercise has not been studied before. A single high dose of inhaled corticosteroid, such as fluticasone propionate (FP), protects against airway obstruction caused by various indirect challenges such as, exercise, eucapnic voluntary hyperventilation and hypertonic saline.

In chapter 3 we analyze the dynamics of spirometry and FOT measurements in EIAO and study the effect of a single dose of fluticasone propionate on the dynamics of EIAO.

The lower and upper airways are connected through neural, immunological and anatomical pathways. Indeed, it has been demonstrated that a stimulus to the upper airway can provoke a response in the lower airways. Direct airway stimuli, such as metacholine, directly interact with receptors in airway smooth muscle, narrowing the airways. Indirect airway triggers, such as exercise and other real life triggers, provoke inflammatory cells, resident in the asthmatic airway wall, to release mediators. These mediators interact with effector cells such as airway smooth muscle, bronchial endothelial cells and mucus producing cells to cause EIAO.

A schematic of the pathways of direct and indirect challenges can be seen in figure 4.

Chronic upper airway inflammation such as allergic rhinitis, frequently prevalent in asthmatic children, may lead to an inflammatory remodeling of the upper airways. The inflamed upper airway tissue can respond to direct stimuli with an inspiratory airflow limitation in asthmatic children and adults. Airflow limitation showed 4 distinct patterns after histamine challenge in asthmatic children as can be seen in figure 5. We speculate that an
indirect airway challenge, such as exercise, may lead to inspiratory flow limitation, similar to that after direct airway challenge. In chapter 4 we analyze inspiratory and expiratory airflow limitation after exercise challenge in dry cold air by measuring the expiratory and inspiratory limb of full flow volume loops.

**DIAGNOSING EIAO**

ATS-ERS guidelines state that, in order to increase the sensitivity of testing, an exercise challenge should commence with an air temperature of maximal 25°C and a relative humidity of maximal 50%\(^2\). However, in a large part of the world, including the Netherlands, real life outdoor situations represent colder and more dry air quality conditions. It is of importance that an exercise challenge test reflects real life circumstances to prevent false negative results and an underdiagnosis and undertreatment of EIAO. The low sensitivity of the exercise challenges performed in accordance with ATS criteria leads to a search for other lung function techniques that can accurately diagnose EIAO in room air conditions. In chapter 5 we will describe the addition of the FOT to enhance the sensitivity of exercise challenge tests to detect EIAO.

In the current guidelines, the control of asthma is advocated to be the target of treatment\(^1\). In the Global initiative for asthma (GINA) guidelines, both the occurrence of EIAO as well as
the asthma control questionnaire (ACQ)\textsuperscript{50} are proposed as tools for measuring the control of asthma. However in children of all ages, there is a poor correlation between questionnaire scores and bronchial hyperresponsiveness after both direct and indirect testing\textsuperscript{51,52}. In chapter 6 we will analyze the relationship between the ACQ and the occurrence of EIAO.

In asthmatic children a higher body mass index (BMI) has been associated with an increased report of exercise induced cough and wheeze\textsuperscript{53}. This may be caused by the high BMI and/or a decreased cardiovascular fitness, as both amplify exercise induced ventilation, which is the trigger for EIAO. However, the report of exercise induced cough and wheeze does not predict the occurrence of EIAO\textsuperscript{11,12}. An increased BMI has been associated with bronchial hyperresponsiveness for both exercise and metacholine\textsuperscript{53-55} In obese adults with asthma adipose tissue leads to a low grade systemic inflammation through the release of adipokines\textsuperscript{56}. These adipokines may also induce inflammation in the airway wall and lead to bronchial hyperresponsiveness. On the other hand, the high BMI asthma child may also be a distinct phenotype featured by enhanced bronchial hyperresponsiveness to exercise\textsuperscript{57}. In chapter 7 we will analyze the relation of body weight and the occurrence and severity of EIAO.

**MAIN GOALS:**

1. Analyze the patency of the airways during exercise in asthmatic children. (Chapter 2)
2. Analyze the effect of a single high dose of inhaled corticosteroids on the dynamics of EIAO. (Chapter 3)
3. Analyze the effect of exercise on the inspiratory flow in asthmatic children. (Chapter 4)
4. Analyze the effect the addition of FOT measurements on the sensitivity and specificity of exercise challenges in warm air to detect EIAO. (Chapter 5)
5. Analyze the association between the ACQ and EIAO. (Chapter 6)
6. Analyze the association between spirometric and anthropometric measurements on the occurrence of EIAO. (Chapter 7)
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