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

Driessen, J.M.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 8

Summary
Summary

Asthma is a common chronic disease which is characterized by episodic airway narrowing and inflammation of the airways and can compromise social and psychomotor development. Exercise, especially in dry and cold air, may induce a transient airway obstructions (EIAO). In this thesis we have investigated this patho-physiological entity and evaluated diagnostic tools to analyze EIAO in children with asthma. A brief introduction of the current standings is given in chapter 1.

NEW FINDINGS IN THE PATHO-PHYSIOLOGY OF EXERCISE INDUCED AIRWAY OBSTRUCTION.

Heavy exercise induces an acute metabolic acidosis which is compensated by a physiological hyperventilation. Nasal breathing facilitates humidification and warming of the inhaled air at the start of exercise however, if the inhaled airflow reaches a threshold larger than the maximal nasal airflow, mouth breathing is necessary to accommodate the increased airflow. As a result, the upper airway is no longer capable to fully humidify and warm the airways. Consequently, intra-thoracic airways become involved in this process, resulting in cooling and drying of the intra-thoracic airways which is believed to be the trigger for airway narrowing 1. The osmotic hypothesis states that drying of the airway wall is the basic trigger for airway narrowing. As this process starts during exercise, the onset EIAO may be during exercise if counterbalancing bronchodilating forces are insufficient 2. According to the vascular hypothesis re-warming of the airway wall after exercise is the basic trigger for airway narrowing, by engorgement of the bronchial wall. Re-warming starts as soon as exercise induced hyperventilation ceases and, as a result, occurs after exercise 3. In chapter 2 we analyzed the patency of the airways during a prolonged, sub-maximal exercise challenge using flow volume loops. In 33 children with asthma we observed 19 cases of EIAO, defined as a fall in FEV1 of more than 15%. Twelve of these children showed EIAO during exercise (breakthrough EIAO), while 7 showed EIAO after exercise (non-breakthrough EIAO). These findings suggest that in the majority of asthmatic children with EIAO airway narrowing starts during and not after exercise. The consequence of these findings is that in asthmatic children dehydration and not heat loss of the airway seems to be the driving force of EIAO. The clinical implication of this find is that asthmatic children who complain of dyspnea during exercise may indeed have EIAO during exercise. Breakthrough EIAO reduces athletic performance, which may result in a low self esteem and quality of life and may also hamper improvement of cardiovascular fitness.

In chapter 3 we evaluated the effect of a single high dose of inhaled corticosteroids on the dynamics of airway narrowing and recovery in EIAO. The protective effect of a single high dose of inhaled corticosteroids has been subject of investigation in recent years 4,5. To evaluate EIAO the FEV1 is routinely used, corresponding with the patency of the larger, conducting airways. Other spirometric indices such as FEF25, FEF50 and FEF75 have been linked with the patency of
respectively larger, conductive and smaller airways. The forced oscillation technique (FOT) is a sensitive and effort independent technique and can determine resistance and reactance of the larger and smaller airways\(^6\). We found that in 12 children with asthma the patency of both the larger and smaller airways fell shortly after exercise followed by a steady recovery of the conducting airways as measured with FEV\(_1\) and FEF\(_{25}\). The smaller airways, as measured with low frequency resistance measurements, FEF\(_{50}\) and FEF\(_{75}\), showed a delayed recovery compared to the larger airways. Inhalation of a single high dose of FP significantly diminished the obstruction of the conducting airways, while the protective effect of FP on the smaller airways was less outspoken. This study implicates that after a rapid airway narrowing following exercise, the recovery of the smaller airways is slower than the recovery of the conducting airways. Fluticasone propionate seems to employ its bronchoprotective effects mainly on the larger, conducting airways. This might be due to the presence of receptors for the used steroid or that the steroid reaches only high enough concentration to trigger the effect in the larger airways.

In asthmatic children, exercise may lead to symptoms suggestive of both lower and upper airway narrowing. Exercise is an indirect trigger of the airways as it induces airway narrowing by the release of mediators from inflammatory cells. A direct stimulus to the airways such as Methacholine may lead to inspiratory as well as expiratory flow limitation in asthmatic children and adults\(^7,6\). It has been hypothesized that this inspiratory flow limitation is the result of chronic inflammation of the upper airways, a frequent co-morbidity in childhood asthma\(^10\). Vocal cord dysfunction (VCD) has also been suggested to cause exercise induced inspiratory flow limitation and can easily be mistaken for EIAO\(^11\). In chapter 4 we analyzed flow limitation following exercise in asthmatic children. 53 of 72 children tested showed an inspiratory and/or expiratory airflow limitation. After exercise, the average fall in FEV\(_1\) was 17.7 ± 14.6%, while the average fall in MIF\(_{50}\) was 25.4 ± 15.8%; no correlation was found between fall in FEV\(_1\) and MIF\(_{50}\) (R\(^2\): 0.04; p=0.717). The fall in FEV\(_1\) peaked 9 minutes and the fall in MIF\(_{50}\) peaked 15 minutes after exercise (5.9 minutes; p<0.001, 99% CI: 2.3 - 9.5 minutes). The inspiratory flow limitation was related to an observed inspiratory stridor while the expiratory flow limitation was related to an observed expiratory wheeze. Of the children showing a flow limitation, 38% (20/53) showed an isolated expiratory flow limitation, 45% (24/53) showed an expiratory and inspiratory flow limitation and 17% (9/53) showed an isolated inspiratory flow limitation. The inspiratory flow limitation we observed peaked well after ceasing exercise and was not accompanied by acute ‘choking’, which both make a diagnosis of VCD unlikely and suggest another cause. More research should be done to analyze the pathological basis of the observed inspiratory flow limitation. This study shows that an exercise challenge can give rise to not only expiratory flow limitation but also inspiratory airflow limitation in asthmatic children. The inspiratory airflow limitation may give rise to persistent asthma like symptoms after exercise and hamper the inhalation of rescue medication.

When analyzing the results of these studies a balance between dilating and constricting forces of the airways before, during and after exercise seems to exist. In rest the parasympathic
nervous system causes minor smooth muscle cell contraction. Periodic sighs (cyclic deep breaths) reduce the airway wall tone through mechanical stretch and counteract smooth muscle cell contraction.

At the start of exercise there is an increase of the patency of the airways, as sympathetic nervous activation downregulates the parasympathetic induced contraction of the airways. Rapid, deep and cyclic breathing stretch the airways, further reducing airway wall tone and enhancing bronchodilation. Cold air induced vasoconstriction may also contribute to the initial increase in patency, especially in the conducting and upper airways.

In asthmatic children, activated mast cells release both bronchoconstricting and bronchodilating mediators during exercise. Prostaglandin E_2, released by mast cells, has a stabilizing effect on the airways and the mast cell, causing bronchodilation. Mast-cells also release histamine, prostaglandine D_2 and leukotrienes causing bronchoconstriction. If the bronchoconstricting forces (histamine, prostaglandine D_2 and leukotrienes) outweigh the bronchodilating forces (prostaglandine E_2 deep and cyclic breathing induced stretch and the reduced para-sympatic activity) the patency of the airways is reduced.

After exercise, as most bronchodilating forces cease, bronchoconstricting forces prevail, further compromising airway patency. A steep fall in airway patency occurs, which peaks immediately after exercise. The congestion of the airways, a consequence of rapid re-warming of the airways takes longer to built up and peaks later after exercise and may be the cause of inspiratory flow limitation.

**NEW FINDINGS IN THE DIAGNOSTICS OF EXERCISE INDUCED AIRWAY OBSTRUCTION.**

A definite diagnosis of EIAO is made with an exercise challenge test in which spirometry before and up to 30 minutes after exercise is measured. Guidelines for exercise challenges limit the humidity of the inspired air to 10 mg·l^{-1} H_2O and a temperature of less than 25°C. A fall in FEV_1 of more than 10% can be used as cut-off for EIAO in the research setting. Analyzing EIAO with FEV_1 requires repetitive, effort dependent, forced breathing manoeuvres which may influence airway mechanics. The forced oscillation technique (FOT) is an effort independent technique which may eliminate the need for repeated forced airway manoeuvres. In chapter 5 we evaluated the addition of the FOT in the analysis of EIAO in warm and cold air in 10 asthmatic children. All children performed 2 exercise challenges on 2 separate days in cold and in temperate air. In cold air the FEV_1 dropped 35.4 ± 16.2% and the resistance at 5 Hz increased 191.1 (23.3; 261.5) %, in temperate air the FEV_1 dropped 15.1 ± 12.1% and resistance at 5 Hz increased 96.2 (9.4; 146.5) %. Using only spirometry, 6 out of 10 cases of EIAO would have been detected, the addition of the FOT allowed detection of 9 of the 10 cases of EIAO in cold air, when testing in temperate air. This study showed that the addition of FOT measurements...
to spirometry when testing EIB in temperate air seems to be helpful to identify the response to exercise in real life, outdoor situations.

In daily clinical practice the report of EIAO is used to assess the level of control of asthma and may alter the therapeutic regimen\textsuperscript{12,13}. However, self reported exercise induced symptoms do not correspond well with the occurrence of EIAO\textsuperscript{14-16}. In the recent update of the global initiative for asthma guidelines (GINA), the asthma control questionnaire (ACQ) is recommended as a tool to measure asthma control\textsuperscript{12}. In chapter 6 we evaluated the relationship between the ACQ and EIAO as both are parameters for control of asthma. Two hundred asthmatic children filled out an ACQ and performed an exercise provocation test in cold air. EIAO was defined as a drop in FEV\textsubscript{1} of more than 15%. Well controlled asthma according to the ACQ was defined by a score of less than 0.75; while poor control of asthma was defined as a score of at least 1.50\textsuperscript{17,18}. The positive predictive value of the ACQ for EIAO was 51% and the negative predictive value of the ACQ for EIAO was 59%. Boys are known to report a more well controlled asthma than girls, which also was true in our analysis. There was no difference in the occurrence of EIAO between genders (p=0.12). The ACQ does not provide conclusive information about the level of control regarding the occurrence and severity of EIAO. It was striking that 41% of children had EIAO despite the fact that according to their ACQ, they were well controlled. This indicates that both tools to assess control of asthma are not interchangeable. Pediatricians should regard the ACQ as a tool which provides complementary information about the control of asthma in children, rather than a defining tool for assessing the control of asthma in daily practice.

In chapter 7 we analyzed the predictive value of several anthropometric, spirometric and oscillometric measurements for EIAO. A high body mass index (BMI) has been associated with the report of exercise induced cough, wheeze and bronchial hyperresponsiveness to metacholine in asthmatic children\textsuperscript{19}. Obese children previously not diagnosed with asthma have an increased risk for EIAO, while children with a relatively low BMI have a reduced risk for EIAO\textsuperscript{20,21}. A normal spirometry before exercise cannot predict the occurrence of EIAO. However, an obstructive pre-exercise flow volume curve, on visual inspection, has been associated with the occurrence of EIB\textsuperscript{22}. FOT is a sensitive tool to measure airway resistance and reactance and may also be able to predict the occurrence of EIAO. In 59 children we found that age and gender corrected BMI z-scores and MEF\textsubscript{50} (% of pred) before exercise predicted the occurrence of EIAO, with respectively odds ratios of 2.7 (p<0.01; CI:1.4-5.1) and 0.96 (p=0.02; CI: 0.93-0.99). There was no correlation between pre-exercise FEV\textsubscript{1} or FOT measurements and EIAO. This study shows that the pre-exercise MEF\textsubscript{50} is an independent predictor for the occurrence of EIB, emphasizing the importance of close examination of the expiratory flow volume loop. Furthermore, we showed that there is a strong association between BMI and EIAO in children with mild to moderate asthma over the full range of BMI’s. These observations are of clinical relevance since they may provide the clinician with new relevant clinical observations to reduce EIAO and improve asthma control.
MAIN CONCLUSIONS

1. In asthmatic children change in the osmolarity of the mucosa and not re-warming of the mucosa is the driving force of exercise induced airway obstruction.
2. Asthmatic children with respiratory symptoms during exercise may indeed have, sometimes severe, airway narrowing during exercise.
3. Pediatricians should regard the ACQ as a tool which provides complementary information about the control of asthma in children, rather than a defining tool for assessing the control of asthma in daily practice.
4. Both the larger, conducting, and the smaller airways contribute to exercise induced airway obstruction.
5. The patency of the larger, conducting airways recover faster than the patency of the smaller airways.
6. A single high dose of fluticasone propionate reduces exercise induced airway obstruction and employs its effect mainly on the conducting airways.
7. Exercise can give rise to inspiratory as well as expiratory airflow limitation in asthmatic children, inspiratory flow limitation peaks later, and is not related to expiratory flow limitation.
8. The forced oscillation technique may be helpful to identify the pulmonary response to exercise in real life, outdoor situations while testing in temperate air conditions.
9. A low $\text{MEF}_50$ and a high BMI are independent predictors of EIAO in asthmatic children.
REFERENCES

1. Carlsen KH, Anderson SD, Bjermer L, et al.; European Respiratory Society; European Academy of Allergy and Clinical Immunology. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. Allergy. 2008 Apr;63(4):387-403. Review.


Summary