Exercise induced bronchoconstriction in childhood asthma
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SUMMARY AND GENERAL DISCUSSION

Exercise induced bronchoconstriction (EIB) has been demonstrated in children as young as 3 years\textsuperscript{1,2}. The clinical features of EIB change with age\textsuperscript{3,4}, and are often poorly recognised by children, parents and even clinicians\textsuperscript{5,6}. On the other hand, exercise induced dyspnea due to lack of cardiovascular fitness may be misinterpreted as EIB, leading to overdiagnosis of asthma. Clinicians therefore face many challenges in identifying, evaluating and treating young children with EIB. This thesis focused on unanswered questions regarding the development, assessment and treatment of EIB in young children.

From bronchiolitis to exercise induced bronchoconstriction

After a general introduction (chapter 1), in which the current insights regarding the relationships between asthma, EIB and viral lower respiratory tract infections (VLRTI) are outlined, chapter 2 compared the clinical pattern in infants <2 years, hospitalised with a respiratory syncytial virus (RSV) or rhinovirus (RV) VLRTI. Hospitalisation for VLRTI in infancy is one of the risk factors for later asthma\textsuperscript{7-9}. RSV and RV are the predominant viruses associated with VLRTI\textsuperscript{10-12}. Several studies compared clinical patterns of RSV and RV VLRTI, but results were inconsistent\textsuperscript{11,13,14}. We compared symptoms and viral load (CT-value) in 120 infants hospitalised with a RSV or RV VLRTI and observed no significant differences in the clinical pattern. Thus on clinical grounds no difference can be made between RSV and RV VLRTI, and hence medical approach should be the same. There was a significant, but weak, relation between viral load and length of hospital stay in children with a RSV VLRTI, whereas viral load in RV VLRTI was not related to length of hospital stay.

The relation between viral load and clinical pattern, and in particular the difference between the predictive value of viral load in RSV VLRTI and RV VLRTI, was further investigated in chapter 3. In this study, we investigated the dynamics of the viral load in 103 infants hospitalised for a RV or RSV VLRTI by performing RT-PCR and determining CT-value on nasal swabs obtained upon hospital admission, discharge and outpatient check-up. We confirmed that viral load at hospital admission was related to length of hospital stay in infants with a RSV VLRTI, as we found in chapter 2. RSV viral load decreased during hospitalisation, which corresponded to other studies investigating viral load in RSV VLRTI\textsuperscript{15-17}. Thus RSV viral load at hospital admission has potential as a prognostic and monitoring measure to predict the clinical course of infants with a RSV VLRTI. In contrast, RV viral load at admission showed no relation with disease severity or length of hospital stay. This difference in dynamics of RSV and RV viral load during VLRTI suggests a different pathophysiological mechanism by which both viruses cause airway disease. Mean CT-value at hospital admission is significantly higher, thus viral load lower, in RV VLRTI compared with RSV VLRTI (chapter 2 and 3), which supports this
hypothesis. We speculate that in RSV VLRTI viral replication induces direct cytopathic effects in the airway, explaining the observed relation between viral load and disease severity. In contrast, disease severity in RV VLRTI might be more related to the severity of the immunopathologic response to the infection, which explains the lack of a relation between viral load and disease severity in RV VLRTI. Genetic predisposition to an immunopathologic response to RV infection may contribute to later airway disease, which could explain the suggested strong relation between RV VLRTI and asthma in later life\textsuperscript{18,19}.

Whether there is indeed a difference in development of asthma in young children with a history of hospitalisation for RSV or RV VLRTI is investigated in chapter 6. In this chapter we described the prevalence and severity of EIB, a specific manifestation of asthma in children. Seventy 5-7 year old children with a history of hospitalisation for RSV or RV VLRTI in infancy underwent an age-adjusted exercise challenge test (ECT). This ECT, using a jumping castle, was designed to assess EIB in young children (chapter 5). EIB was diagnosed in 37\% of the children, which is approximately 4 times more than the prevalence of asthma in the general population of Dutch children <12 years of age (maximal 10\%\textsuperscript{20}). Clinicians should be aware of this high prevalence of EIB in young children with a history of hospitalisation for VLRTI, especially since EIB is hard to recognise in this patient group\textsuperscript{5,6}. The later is confirmed by the low frequency of parent-reported exercise induced symptoms in the children with a positive ECT in this study. We did not find a favourable asthma outcome in young children (median 5.6 years) with a history of RSV VLRTI compared with RV VLRTI, which was observed in several other studies performed in older children\textsuperscript{18,19,21,22}. Children with a history of hospitalisation for RSV VLRTI in our study even had a lower baseline pulmonary function compared to children with a history of RV VLRTI. A possible explanation for the discrepancy in outcomes of RSV and RV VLRTI could be that the association between RSV VLRTI and subsequent airway disease decreases steadily with increasing age\textsuperscript{23}; a history of RSV VLRTI is associated with increased risk of wheezing till age 10, which isn’t significant anymore by age 13\textsuperscript{24}. The low pulmonary function of children after RSV VLRTI as we observed, is compatible with this theory. The young child with impaired pulmonary function after RSV VLRTI suffers from asthma symptoms, but might overcome airway disease with ageing, as the airways develop and airway calibre increases.

Whether a VLRTI in infancy damages the airways and/or alters the immunologic response to cause later airway disease, or simply reveals susceptible infants rather than directly cause asthma remains a topic of discussion. These different hypotheses are not mutually exclusive and probably the combination of a severe VLRTI in a pre-existing susceptible infant accounts for the development of airway disease in later life\textsuperscript{7}. 
Assessment of exercise induced bronchoconstriction in young children

There is a widely held belief that EIB occurs after cessation of exercise. Clinicians therefore may tend to explain asthmatic symptoms during exercise as non-asthmatic in origin. However in asthmatic children, pulmonary function is often already substantially decreased 1 minute after a regular exercise challenge of 6 minutes, suggesting that the onset of EIB in children could be during exercise. In adults, only prolonged (>15 minutes) exercise can trigger EIB during exercise.[25,26] Pulmonary function, as measured by FEV₁, during exercise in asthmatic children has not been investigated before. In chapter 4 we measured pulmonary function before, during and after a prolonged exercise test of 12 minutes duration in 33 asthmatic children, aged 8-15 years. Whilst running on a treadmill, single flow volume curves were measured each minute during exercise for a maximum of 12 minutes or until a fall in FEV₁ >15% from baseline value had occurred. Spirometry was repeated after exercise. Out of 19 children with EIB, defined as a post-exercise fall in FEV₁ >15%, 12 children showed bronchoconstriction during exercise. This ‘breakthrough EIB’ occurred between 6 and 10 minutes of exercise, with a further deterioration of FEV₁ after cessation of exercise.

Breakthrough EIB is probably due to an imbalance between the bronchoconstricting and bronchodilating influences during exercise. Apparently the bronchoprotective effect of exercise, through the release of nitric oxide and prostaglandins, and stretching of airway smooth muscle, is short-lived in children with breakthrough EIB, and rapidly followed by bronchoconstriction. The quick onset of breakthrough EIB in children is not compatible with the thermal hypothesis, which suggests that EIB is caused by rapid rewarming of the airways after the cessation of exercise. The thermal phenomenon, however, may contribute to EIB and may explain the protracted recovery seen in asthmatic adults.

The finding that breakthrough EIB frequently occurs in asthmatic children is of clinical importance. Breakthrough EIB can result in dropping out during exercise, which lowers self-esteem and leads to avoidance of exercise with consequently deterioration of cardiovascular condition. Clinicians should be aware that symptoms of dyspnea during exercise in children may well be caused by EIB.

Breakthrough EIB was further investigated in chapter 5. In this chapter we described a novel ECT, designed to investigate EIB and breakthrough EIB in 5-7 year old children. Few studies have documented EIB in children <8 years, and described high ECT failure percentages (~15%) due to difficulties with spirometry and sustaining the exercise challenge¹. Free-run tests are often used to assess EIB, however in young children forced running might be overwhelming and duration of running seems to be limited by age¹. Seeking for a mode of exercise that is sustainable, safe, and sufficiently vigorous to maintain a heart rate above 80% of predicted maximum (according to ATS criteria), we designed an ECT using a jumping castle. The ECT consisted of jumping on a jumping
castle for 6 minutes. Pulmonary function was measured before, during and after exercise. Eighty-two children performed our ECT and all of the children were eager to jump on the jumping castle. In 7% of the children the ECT could not be performed reliably, mainly due to technical difficulties performing spirometry.

Besides concluding that an ECT using a jumping castle is suitable, effective and safe for diagnosing EIB in young children, our study showed that breakthrough EIB also occurs in many young asthmatic children. In young children with breakthrough EIB, mean pulmonary function rapidly decreased during exercise, in some children even within 2 minutes. Children with breakthrough EIB had a lower baseline pulmonary function, a more severe fall in post-exercise pulmonary function and a slower recovery from EIB compared with non-breakthrough EIB. Breakthrough EIB can therefore be regarded as a sign of uncontrolled asthma, severely compromising children in performing exercise.

The rapid onset of breakthrough EIB in young children corresponds to the age-related time course of EIB; the younger the child, the shorter the time to maximal bronchoconstriction after exercise and the quicker the recovery from EIB\textsuperscript{1,3,4}, which our study confirmed and extended on. The mechanism responsible for this age-related pattern is unknown. Young children may be prone to rapid airway dehydration, as their minute ventilation is relatively high and their capacity to humidify the inspired air low compared with adults\textsuperscript{27,28}. Swift changes in osmolarity probably result in a faster release of inflammatory mediators. Furthermore, airway smooth muscle in young children might have a shortened response and relaxation time, which may also play a role in breakthrough EIB\textsuperscript{1}. This airway ‘twitchiness’ might wane with ageing, as asthmatic airways remodel and the airway smooth muscle cytoskeleton stiffens.

Chapter 8 is a review article, addressing difficulties clinicians might face in recognising and evaluating children with EIB. In this chapter recommendations for the assessment of EIB in children and adolescents are made, based on current literature.

Although exercise can trigger the classic symptoms of asthma, in children symptoms can be subtle and nonspecific. Parent- and child-reported symptoms weakly correlate with the presence and severity of EIB\textsuperscript{5,29}, which we have also shown in chapter 5. Therefore questionnaires that measure asthma control by self-reported symptoms should be interpreted with care. On the other hand, some exercise induced symptoms might be mistaken for EIB and can be due to dysfunctional breathing, lack of cardiovascular fitness, or other cardiopulmonary disease. For example, most children with EIB cough, but this symptom is not specific for EIB\textsuperscript{30}. The weak relation between exercise induced symptoms and EIB in children stresses the need to use bronchial provocation tests. A suggestion for the assessment of children with exercise induced dyspnea is shown in figure 1.
An ECT is the first choice of bronchial provocation test to assess EIB in children, since it is a “real-life” test, providing direct insight into the severity and course of a child’s EIB. The usual protocols for assessing EIB require important adjustments for use in young children, because the time to maximal bronchoconstriction and recovery from EIB in children is age-dependent. Moreover, young children have a short attention span and easily fatigue as a result of repeated forced breathing manoeuvres. We therefore recommend an appropriate timing of post-exercise pulmonary function measurements, including measurements in the first 5 minutes post-exercise to prevent false-negative results. Pulmonary function in most 3-7 year old children recovers within 15-20 minutes, which allows earlier termination of pulmonary function measurements compared with an adult ECT. Although $FEV_1$ is recommended as the primary spirometric variable for detecting EIB, in children <7 years, $FEV_{0.5}$ is likely to be more reliable since most young children are unable to perform the required full forced expiration during a total second. With an age-adjusted protocol, an ECT can even be performed in children as young as 3 years of age. However, sometimes alternative challenge tests or pulmonary function measurements, such as the forced oscillation technique, are necessary to assess bronchial hyperresponsiveness in children.

Figure 1. Flow chart for the assessment of children with exercise induced dyspnea. *Adopted from werkboek kinderlongziekten.* Such as allergic rhinitis, atopy, family atopy, pulmonary function abnormalities (anomaly flow volume curve, reversibility, $FEV_1$ <70% predicted). Indirect provocation tests such as exercise challenge test and mannitol test are specific for asthma. Restart flow diagram (left arm). *Note: asthma and dysfunctional breathing can coexist.*
Assessing pulmonary function during exercise to identify breakthrough EIB can provide important information about the severity of a child’s EIB. Moreover, measuring breakthrough EIB could prevent severe and uncontrolled falls in post-exercise pulmonary function that can occur during a regular ECT. Potentially, a breakthrough ECT could be used as a dose-response bronchial provocation test, in which time to the occurrence of breakthrough EIB can be considered as the degree of airway hyperresponsiveness.

**Exercise induced bronchoconstriction and obesity**

There is an abundance of cross-sectional studies demonstrating an association between overweight and EIB, however there is a paucity of prospective intervention studies in children. In chapter 7 we prospectively investigated the effect of dietary induced weight loss on EIB in overweight asthmatic children. Obesity in asthmatic children is associated with more severe EIB compared with non-obese asthmatic children\textsuperscript{33,34}, but the effect of weight loss on asthma outcomes in obese asthmatic children was not investigated yet. Twenty children (8-18 years) with EIB and moderate to severe overweight followed a diet based on healthy daily intake for 6 weeks. Before and after the diet period they performed an ECT. Besides a significant reduction in weight and BMI, mean severity of EIB significantly improved after the diet period. The reduction in BMI z-score was related to the improvement of EIB in children that lost weight.

The beneficial effect of weight loss on EIB might be the result of improvement of chest wall mechanics and tidal volumes, which facilitate deep inspirations and subsequent airway smooth muscle relaxation. Weight loss may also decrease systemic inflammation, since obesity is considered an inflammatory state with increased levels of hormones, chemokines and cytokines, which can play a role in airway inflammation.

The finding that even a small reduction in BMI improves severity of EIB, indicates the potential importance of weight management in the treatment of the overweight child with asthma.
REFERENCES


