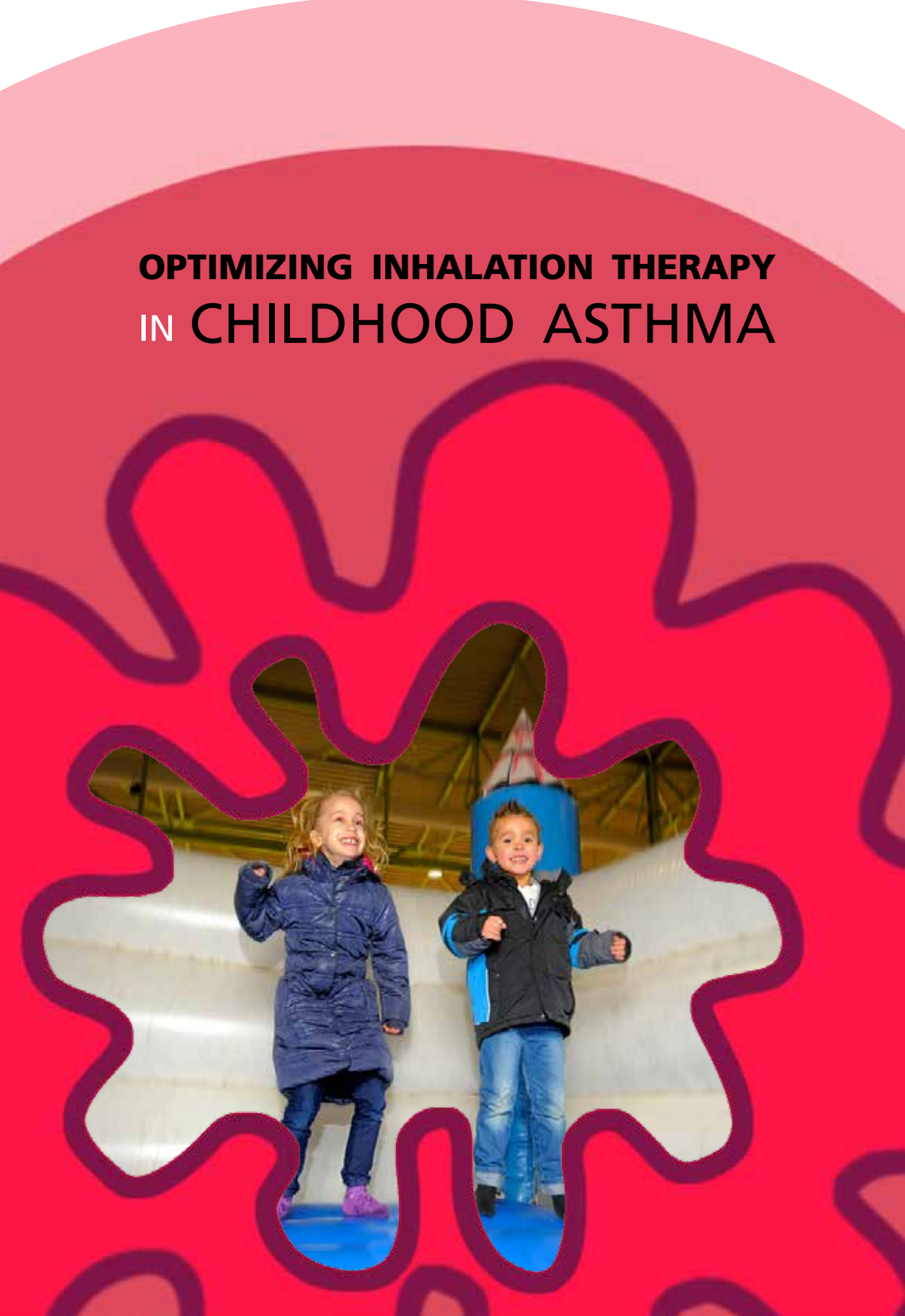
OPTIMIZING INHALATION THERAPY IN CHILDHOOD ASTHMA



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OPTIMIZING INHALATION THERAPY IN CHILDHOOD ASTHMA

DISSERTATION

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the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
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Contents

Chapter 1

General introduction

INTRODUCTION

Asthma is a common chronic disease, featured by airway hyperresponsiveness (AHR), which leads to recurrent episodes of wheezing, breathlessness, chest tightness and/or cough. Worldwide there are approximately 300 million individuals affected with asthma and the prevalence can range up to 18% of the population [1-3]. In children 13-14 years old, prevalence of asthma symptoms range up to 36% [1]. As many as 50% of infants experience at least one episode of wheezing during the early years of life and asthma will be diagnosed in one third of these children by the time they are six years of age [4]. Although chronic airway inflammation is the hallmark of asthma, there is a large inter-individual variability, which is expressed in the clinical presentation, response to medication, and to bronchoprovocation tests (BPT's) in asthmatic patients.

Childhood asthma

Many disorders can mimic asthma symptoms in childhood such as upper airway diseases, poor cardiovascular fitness, and dysfunctional breathing. Frequently, these disorders coexist and influence each other. Diagnosing asthma can be a challenge, especially in young children, as symptoms tend to be less specific than in older children and there is no golden standard. Although in children over eight years usually a trial of medication is used to confirm a diagnosis of asthma, an indirect BPT with mannitol or exercise can be used to diagnose airway hyperresponsiveness [5-9]. A direct bronchoprovocative test with methacholine or histamine is not a valid tool to confirm a diagnosis of asthma as it is not specific and will be positive in children with other airway diseases such as allergic rhinitis and airway infections.

Spirometry assesses the flow and volume during a forced in- and expiration and is the most common pulmonary function measurement performed in asthmatic children [10]. Reversibility of pulmonary function can be tested by inhaling salbutamol after a baseline measurement and is used to diagnose and to monitor asthma. Significant reversibility of spirometry to salbutamol is a specific, but not sensitive tool to identify childhood asthma.

Treatment of asthma

Most asthmatic children can achieve well controlled asthma if they use inhaled corticosteroids (ICS) with an appropriate inhalation technique on a daily basis. However, parents and children perceive daily use of medication as a large burden especially because many children have seemingly symptomless periods. Motivating parents and children to adhere to their medication is a key issue in asthma management. Non-adherence to inhaled medication of children or their parents (if the patient is a young child) has a detrimental influence on the efficacy of ICS therapy. The most basic form of non-adherence is when patients do not understand the rationale for treatment (unintentional non-adherence). Although this can be easily overcome by providing appropriate information, studies consistently show that education alone is insufficient to improve adherence, indicating that other factors are more important in driving non-adherence [11]. Unintentional non-adherence is often related to barriers to achieve adherence such as limited

family routines (forgetting to take the medication), and child raising issues, i.e. parents are unable to consistently administrate medication to their child. Intentional non-adherence refers to patients who deliberately choose not to follow the doctor's recommendations, often based on the illness perceptions of their child and medication beliefs. Such perceptions and beliefs have consistently been shown to be strong determinants of adherence [11]. For example, parents may overestimate disease control because they do not recognize symptoms of their child's disease, which may diminish their perception of the need of daily ICS use [2,12,13].

Exercise induced bronchoconstriction

Exercise is a common trigger of AHR and causes the classic symptoms of asthma; coughing, wheezing and chest tightness. However symptoms can be subtle and aspecific, children can avoid exercise and not have symptoms at all. Exercise induced bronchoconstriction (EIB) is characterized by expiratory airflow obstruction and is a highly specific and frequent symptom in childhood asthma. It reflects asthmatic airway inflammation and can be seen as a sign of uncontrolled asthma [14]. EIB is a symptom of childhood asthma and not a separate disease as it can be in adults [15]. EIB occurs in up to 23% of school children and has serious repercussions on the quality of life of these children. EIB reduces the participation in sports and play in children with asthma and 79% experience EIB as the most bothersome aspect of their asthma [16,17].

The exact pathophysiology of EIB remains uncertain. However, two hypotheses for its pathogenesis have been proposed. One assumes that exercise-induced hyperpnea dries the epithelium, leading to hyperosmolarity of the airway surface fluid, causing release of histamine from mucosal mast cells resulting in bronchial obstruction [18,19]. Indeed exercise in a humid environment makes the airway response to exercise disappear completely. The second hypothesis states that exercise-induced hyperventilation could result in airway cooling and vasoconstriction. After exercise, with normal ventilation, airways rapidly re-warm leading to vascular engorgement and mucosal edema, resulting in bronchial obstruction [20]. Strongly arguing against the vascular hypothesis is the breakthrough phenomenon, which is the occurrence of airway narrowing during exercise [21]. Both hypotheses do not exclude each other, and more progressed airway inflammation may lead to a stronger contribution of vascular phenomena to airway narrowing, as hypervascularity has changed the structure of the airway wall.

An exercise challenge test (ECT) is an indirect BPT that detects EIB and can identify asthma and evaluate asthma treatment [22]. EIB is defined as a fall in FEV_1 (or $FEV_{0.5}$ if FEV_1 is not appropriate) ≥13% following exercise [23]. When parents attend their child's ECT and the test result is discussed with them, they may recognize their child's symptoms, and start to realize their child's limitations in play and sports. This could motivate parents to adhere to the prescribed drug regimen. Improving medication beliefs and illness perceptions may motivate parents to improve adherence. Our clinical impression is that discussing the result of an ECT can have a vast impact on parent's awareness of their child's symptoms especially when children are unexpectedly diagnosed with EIB [21,24]. In **chapter 2** we analyzed the influence of discussing the result of an ECT on adherence to maintenance medication, parental illness perceptions and medication beliefs in young children with asthma.

Treatment of EIB

Because of their potent anti-inflammatory effects, inhaled corticosteroids are the cornerstone of asthma treatment and are recommended for daily use in children with moderate to persistent asthma [25]. Correct use of inhalation devices is a prerequisite for successful drug treatment of asthma and errors in inhalation technique are associated with poor asthma control [25-28]. However, inhaler technique is inadequate in many asthmatic children and even after inhalation instruction many children use their inhaler devices too poorly to result in reliable drug delivery [27,29,30]. International guidelines recommend repeated comprehensive inhalation instructions every three-six months to improve inhalation technique [1,29,31] . In **chapter 3** we analyzed the sustained effect of inhalation instruction on inhaler technique six weeks after instruction in young asthmatic children already using a pressurized metered dose inhaler with a spacer device.

Deposition of inhaled medication in the upper airway compromizes deposition at the target area. This upper airway deposition is caused by the sharp angle between the pharynx and the trachea [32,33]. In asthmatic children the deposition of the inhaled medication may even be further compromized because the upper airway is smaller and has a different geometry, compared to adults. Even with optimal inhalation technique via a breath actuated inhaler, 50-60% of the dose of beclomethasone dipropionate (BDP) impacted in the oropharynx in children under the age of 12, as measured in a radio-labeled study [34]. Brandao et al. showed that inhaling nebulized bronchodilators in a forward leaning body posture during an asthma exacerbation in young asthmatic adults, led to a faster recovery of lung function compared to the conventional body posture [35]. They suggested that this could be caused by a higher pulmonary deposition of the nebulized medication in the forward leaning posture. We hypothesized that stretching the bend in the upper airway during inhalation could improve the effect of salbutamol on lung function. In **chapter 4** we analyzed the reversibility of lung function in asthmatic children in a pilot study after a single regular dose of 200µg salbutamol either inhaled in the forward leaning body posture with the head flexed backwards or in the standard body posture.
In **chapter 5** we further explored this topic in a cross-over randomized controlled study in which children performed spirometry to assess reversibility four times, twice with 200µg salbutamol and twice with 400µg salbutamol (both doses once in the standard body posture, once in the forward leaning body posture).

In **chapter 6** we analyzed the protective effect against EIB of a single low dose of 200µg BDP inhaled four hours before an ECT with a forward leaning body posture with the head flexed backwards compared to the standard body posture.

Daily use of ICS reduces EIB in asthmatic children. A previous study also showed an acute protective effect of a high single dose of ICS in asthmatic children not currently treated with inhaled corticosteroids [36]. The effect, however, of a low single dose of ICS against EIB is unknown. In **chapter 7** we analyzed the protective effect of a single dose of 200µg BDP inhaled with a breath actuated inhaler four hours prior to an ECT against EIB.

A recent study showed that in children with asthma, exercise not only triggered EIB but also induced post exercise *inspiratory* flow limitation [24]. The pathophysiology of inspiratory flow limitation is unclear. Salbutamol provides excellent protection against EIB, but the effect on inspiratory flow limitation is unknown. The bronchoprotective effect of salbutamol in EIB is largely attained by its stabilizing effect on mast cells. [19,24]
In **chapter 8** we analyzed if and to what extent salbutamol can protect against exercise induced inspiratory flow limitation and whether this protection is related to exercise induced expiratory flow limitation.

At present, there is a lack of diagnostic tools to assess individual responsiveness to various therapies. No asthma treatment currently available provides benefit to all children, and a substantial number of children will not respond to any therapy [37]. It is a critical clinical question whether a particular therapy will be effective in an individual child with symptoms of asthma. In **chapter 9** we analyzed the relationship between change in mannitol PD_{15} (provoking dose of mannitol to cause a ≥ 15% fall in FEV_1) 6 hours after a single dose of BDP, and after 4 weeks of treatment with BDP.

MAIN GOALS

Adherence and inhalation technique;

I. Analyze the impact of a discussed ECT on the adherence, medication beliefs and illness perceptions of parents in young asthmatic children.
II. Analyze the sustained effect over time of an inhalation instruction on inhalation technique in young asthmatic children using a pressurized metered dose inhaler with a spacer device.

Body postures during medication inhalation;

III. Analyze the effect of inhaling salbutamol in a forward leaning body posture compared to a standard body posture on reversibility of spirometry in asthmatic children (pilot study).
IV. Analyze the effect of inhaling salbutamol in different doses and in a forward leaning body posture on reversibility during spirometry in asthmatic children.
V. Analyze the effect of inhaling a low single dose of an ICS in a forward leaning body posture versus the standard body posture on EIB in asthmatic children.

Medication;

VI. Analyze the protective effect of a low single dose of an ICS against EIB.
VII. Analyze the protection of a single dose of salbutamol against exercise induced inspiratory flow limitation in asthmatic children.
VIII. Analyze the effect of a single dose of an ICS on mannitol responsiveness as a predictor of the effect of regular beclomethasone treatment.

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Chapter 2

The impact of discussing exercise test results of young asthmatic children on adherence to maintenance medication

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ABSTRACT

Objective

Parents' awareness of their child's asthma may improve by discussing an exercise challenge test (ECT) result with them. We investigated the influence of discussing an ECT result with parents on adherence to inhaled maintenance medication, parental illness perceptions and medication beliefs in young asthmatic children.

Methods

A total of 79 children, 4–7 years old and enrolled in our standard comprehensive asthma care program, performed an ECT to assess exercise induced bronchoconstriction (EIB). The result of the ECT was immediately discussed with the parents. Median medication adherence level was measured with electronic medication loggers from six weeks before the ECT till six weeks afterwards. Parental beliefs about medicines and illness perceptions were measured with the Beliefs about Medicines Questionnaire (BMQ) and the Brief Illness Perceptions Questionnaire (B-IPQ).

Results

The median baseline adherence level was high (83%) and showed a small significant decline after the ECT. There was no significant difference in the decrease in median adherence level between the children with or without EIB. Most parents (82.1%) showed a positive necessity–concern ratio at baseline, as measured with the BMQ. There was no clinical relevant change in medication concerns and necessity scores or in illness perceptions.

Conclusion

Discussing ECT results with parents does not modify median adherence levels to inhaled maintenance medication nor medication beliefs of highly adherent young asthmatic children who are already enrolled in a comprehensive asthma care program.

INTRODUCTION

Most children with asthma can achieve well-controlled asthma if they use their inhaled corticosteroids (ICS) on a daily basis. Non-adherence, however, has a detrimental influence on the efficacy of ICS therapy [1–3]. One of the reasons for non-adherence is that patients (and their parents, if the patient is a child) do not understand the rationale for treatment. Although this can be overcome by providing appropriate information, studies consistently show that education alone is insufficient to improve adherence, indicating that other factors are more important in driving non-adherence [4]. A distinction can be made between unintentional and intentional non-adherence. Unintentional non-adherence is related to barriers to achieve adherence such as limited family routines and child-raising issues. Intentional non-adherence refers to patients who deliberately choose not to follow the doctor's recommendations, based on their illness perceptions and medication beliefs. Such perceptions and beliefs have consistently been shown to be strong determinants of adherence [4]. For example, parents may overestimate disease control because they do not recognize symptoms belonging to their child's disease, which may diminish their perception of the need of daily ICS use [1,5,6].

Exercise induced bronchoconstriction (EIB) is one such symptom, which is frequently not recognized by caregivers (especially in young children) as symptoms may be subtle [7]. An exercise challenge test (ECT) can be used for diagnosing and monitoring asthma, as well as educating parents about the symptoms of their child [8]. Our clinical impression is that discussing an ECT result with parents can have a significant impact on parent's awareness of their child's symptoms, especially when children are unexpectedly diagnosed with EIB [9,10]. We hypothesized that demonstrating EIB in a child may change parental perceptions about the need to use ICS and subsequently increase adherence.

The aim of our study was to evaluate the effects of discussing ECT results with parents on adherence to inhaled maintenance medication and on parental illness perceptions and medication beliefs.

METHODS

Patients

We included young asthmatic children in a prospective intervention study, in which we assessed adherence to ICS, parental illness perceptions and medication beliefs before and after an ECT result was discussed with the parents. The children without a diagnosis of EIB served as controls for the children with EIB, as we wanted to assess the influence of the discussed outcome of the ECT on adherence.

Patients aged 4–7 years, with a doctor's diagnosis of persistent mild to moderate asthma, a prescription of ICS and no experience with performing an ECT, were recruited from the outpatient clinic of the pediatric departments of three hospitals (Medisch Spectrum Twente, Enschede (MST) and Ziekenhuisgroep Twente (ZGT), Hengelo and Almelo). In our asthma clinics, comprehensive asthma management consists of 30 min consultation for newly referred patients and 15 or 30 min consultation for follow up visits, every 3–6 months to alternately a pediatrician or a nurse practitioner. During these consultations adherence is structurally assessed and

education is provided to children and their parents on various aspects of self-management of asthma.
Children using metered dose inhalers (MDIs) not compatible with the adherence loggers or with other pulmonary or cardiac disorders were excluded. Children being admitted to the hospital or being prescribed systemic corticosteroids, because of an exacerbation in the last four weeks prior to the ECT, were excluded or included eight weeks later.

Exercise challenge test
The ECT was performed as previously described by van Leeuwen et al. [9]. In summary, children jumped for 6 min on a jumping castle in cold, dry air conditions (9.5–10 °C and humidity 57–59%) in an indoor ice skating rink. Their heart rate was continuously monitored by a radiographic device and the target was to achieve 80% of maximum heart rate (80% x(220 – age)). Their pulmonary function was measured with the aid of a Microloop MK8 Spirometer (ML3535) before, during and after exercise using standard European Respiratory Society protocol [11]. An exercise induced fall in forced expiratory volume in 0.5 s ($FEV_{0.5}$, percentage of predicted based on the reference values of Koopman et al [12]) of ≥13% compared to baseline was considered as positive for EIB [13].
After the ECT, the result of the test was discussed in a structured way, i.e. a fall of lung function of ≥50% indicating severe EIB, 25–50% moderate EIB and 13–25% mild EIB. We discussed observed exercise induced asthma symptoms and effects of inhaled medication on the symptoms with parents.

Adherence measurement
Adherence was measured from six weeks before until six weeks after the ECT by validated electronic medication loggers (Smartinhaler® Nexus6 Ltd, Auckland, New Zealand, or the Doser™, Meditrack products, South-Easton, MA [14]). Smartinhalers® save date and time of each actuation and Dosers™ save the number of actuations per day. Adherence was calculated as the number of inhaled doses and expressed as a percentage of the number of doses prescribed. For a twice daily regimen, each dose had to be given within an interval of 6 h around the prescribed dosing time (8 AM and 5 PM). For a twice daily regimen with use of the Doser™, time interval was impossible to analyze and two actuations a day were deemed good adherence. Medication using less than 80% of prescribed dosages was deemed poor adherence and 80% or more as good adherence [15,16].

Questionnaires
Parental illness perceptions and medication beliefs were assessed by the Brief Illness Perception Questionnaire (B-IPQ) and the Beliefs about Medicines Questionnaire (BMQ) [17,18]. Asthma control was assessed by the Childhood Asthma Control Test (C-ACT) [19]. Children and parents completed these questionnaires when they received their medication logger six weeks before the ECT and when they returned their loggers six weeks after the ECT. The C-ACT was also completed after finishing the ECT. All questionnaires were completed by the same parent during the study.

The B-IPQ comprises of eight questions, each on a scale from 1 to 10, assessing parental perceptions about their child's asthma. All questions were analyzed individually. The BMQ consists of five questions about perceived needs and five questions about concerns (Likert scale with scores 1–5) about maintenance medication, offering the possibility to calculate a necessity/concern ratio. High parental perceived necessity of maintenance medication is represented by low necessity scores, while high parental perceived concerns of maintenance medication were represented by low concern scores. The C-ACT is especially designed to measure asthma control in asthmatic children 4–11 years old and consists of seven questions; four questions to be filled out by the child (scores 0–3) and three to be filled out by the parents (scores 1–5). Scores of all questions were summed (range 3–27) and a C-ACT score of ≤19 indicates poor asthma control.

Educational level

Parental educational level was assessed by the number of years of formal education post primary school comparable to Melani et al. and Apter et al. [20,21]. The data were dichotomised and classified as low or high (<9 or ≥9 years of formal education post primary school). Primary education in the Netherlands implies eight years of education during the age of 4 till 12 years.

Sample size calculation

We considered an increase of 15% in adherence to be clinically relevant. From a hypothetical baseline mean adherence of 60% with an alpha of 5% and a power of 80%, 59 subjects with a fall in $FEV_{0.5}$ of ≥13% were needed [22]. A previous study, with the same design, showed that 70% of asthmatic children showed a fall in $FEV_{0.5}$ ≥13% [10]. Therefore, we aimed to enroll 84 children.

Statistical analyses

Data were presented as means with standard deviation (SD) or as median with interquartile range (IQR), depending upon the distribution for continuous variables, or as numbers with percentages (%) for categorical data.

Within-person changes in continuous variables (e.g. adherence) were analyzed with a paired *T*-test or a Wilcoxon signed rank test, as appropriate. Between-group differences in continuous variables were analyzed with the analysis of variance or a Kruskall Wallis test, as appropriate. Between-group comparisons of nominal or ordinal variables were performed by Chi-square tests. For the analysis of correlated proportions, a McNemar test was used. To assess the correlation between two continuous variables Pearson's correlation coefficient or Spearman's rho were computed, as appropriate.

Data were analyzed with SPSS® for Windows® version 15 (IBM, Chicago, IL) analytical software. A two-sided value of $p<0.05$ was considered statistically significant.

Ethical considerations

This study was approved by the hospital ethics review board. All parents provided written informed consent to participate in this study.

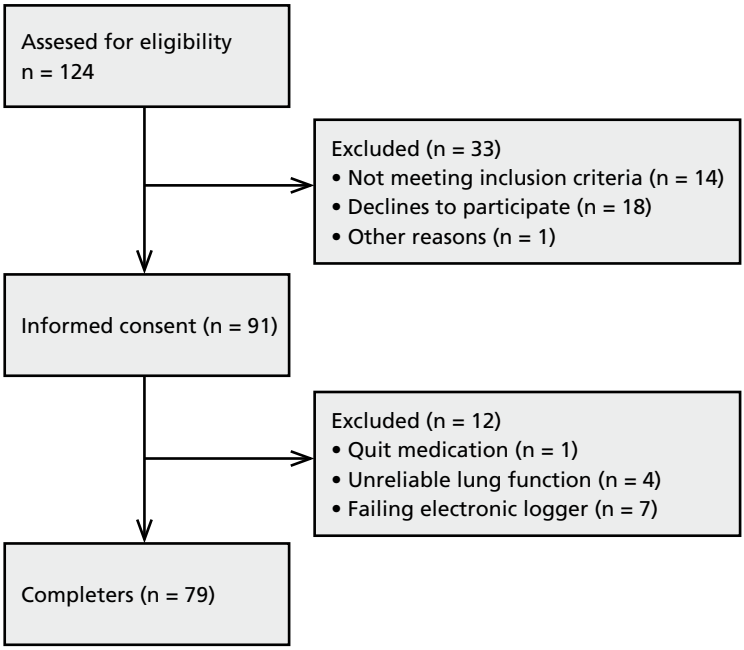

Figure 1. Flow chart of inclusion.

RESULTS

Of the 124 eligible children, 91 entered the study after informed consent was obtained and 79 (median age 5.9 years) were analyzed (Figure 1).
Of these 79 children, 43 (54.4%) had been hospitalized because of an asthma exacerbation before. Approximately two-thirds of the parents had a low educational level. At inclusion 46 (59%) of 78 (1 missing questionnaire) had well-controlled asthma (Table 1).

Exercise challenge test

All the children achieved their target heart rate during the ECT. Forty-two children (53.2%) showed EIB after the ECT. They had a mean fall in $FEV_{0.5}$ of 23.9 ± 10.7% and a mean baseline $FEV_{0.5}$ of 79.1 ± 12.0% of the predicted value. The children without EIB had a mean fall in $FEV_{0.5}$ of 7.4 ± 8.0% and a significantly higher baseline $FEV_{0.5}$ of 85.6 ± 11.6% compared to the children with EIB (difference 6.5% (95% CI 1.2%, 11.8%); $p = 0.017$).

Adherence

The median adherence in the baseline period before the ECT was 83.0% (IQR 57.1–94.4%) and was similar in children with (86.4%, IQR 57.1–92.4%) and without EIB (80.9%, IQR 59.3–97.0%, $p = 0.753$). Forty-four children (55.7%) showed good adherence (≥80%). The median adherence showed a small but statistically significant decrease in the period after the ECT (5.1%, 95% CI 1.4%, 8.9%; $p = 0.008$), which was more pronounced in the children without EIB compared to the children with

Table 1. Characteristics of study patients.

Number of patients	79
Patient characteristics	
Age, years	5.9 (5.4–6.9)
Boys	45 (57%)
Hospitalization ever before study entry	43 (54.4%)
Asthma diagnosis (years)[a]	1.7 (0.3–3.2)
Maintenance medication	
ICS	76 (96.2%)
ICS + LABA	3 (3.8%)
LTRA's	11 (13.9%)
Asthma control	
$FEV_{0.5}$ (% predicted)	82.1 ± 12.2
C-ACT baseline score[b]	20.5 ± 4.2
Questionnaires	
BMQ positive necessity–concerns ratio	64 (82.1%)
Low maternal educational level[c]	53 (67.1%)
Low paternal educational level[c]	54 (68.4%)

Data expressed as mean values ± standard deviation, median with interquartile ranges or numbers (percentage).

[a] Asthma diagnosis: period of treatment for asthma by a pediatrician. ICS: inhaled corticosteroid; ICS + LABA: inhaled corticosteroid and long-acting ß2–agonist combination; LTRAs: leukotriene receptor antagonists. $FEV_{0.5}$: forced expiratory volume in 0.5 s, percentage of predicted based on the reference values of Koopman et al. [12]; BMQ positive necessity–concerns ratio: 1 missing. The BMQ consists of 5 questions about perceived need and 5 questions about concerns (Likert scale with scores 1–5) about maintenance medication offering the possibility to calculate a necessity/concern ratio.

[b] C-ACT: Childhood-Asthma Control Test: a score ≤19 indicates uncontrolled asthma [19].

[c] Low educational level is defined as <9 years education post primary school.

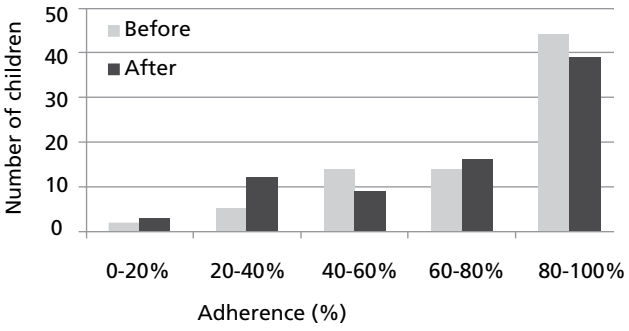

Figure 2. Adherence of the total study group (79 children) before and after the exercise challenge test.

EIB (2.8% vs. 7.7%, 95% CI -2.6%, 12.4%; p = 0.197). The change in adherence was similar in children with poor adherence (<80%) and good adherence (≥80%) at baseline (-4.1 ± 21.7% vs. -6.0 ± 11.7%, difference 1.9% (95% CI -9.5%, 5.7%), p = 0.62). Adherence before and after the ECT is shown in Figure 2.
Baseline adherence and change in adherence were not determined by patient characteristics (data not shown). Maternal and paternal educational levels were not related to baseline adherence (p = 0.185 and 0.845, respectively).

BMQ
At baseline 64 (1 missing, 82.1%) of 78 parents showed a positive necessity–concerns ratio as measured with the BMQ, indicating that their perceived necessity outweighed their concerns; at the end of the study this ratio increased to 68 (87.2%, p = 0.424) of 78. There was a small, but significant decrease in the necessity–concerns ratio in the total study group (-1.24 ± 3.5 (95% CI 0.45, 2.04); p = 0.003) and this decrease was similar in the EIB and non-EIB-group (p = 0.99). The baseline BMQ necessity and concerns scores were neither associated with baseline adherence, nor were changes in necessity–concerns ratio associated with changes in adherence (all p 0.064).

B-IPQ
Of the eight illness perceptions at baseline (as assessed by the B-IPQ), only perceptions about treatment control showed a weak correlation with baseline adherence (r = 0.23, p = 0.042). Nearly all illness perceptions showed a small statistically significant change from baseline of approximately 1 unit. All changes were towards less consequences, more personal and treatment control, less concerns and less emotional feelings. Only the decrease in concerns regarding the illness showed a weak correlation with less decrease in adherence (r = -0.22, p = 0.048). These findings were similar for children with and without EIB.

C-ACT
At baseline, 59.0% of the 78 children (1 missing) showed well-controlled asthma according to the C-ACT, compared to 85.9% at the end of the study (p<0.001). There was no correlation between baseline adherence and asthma control at the end of baseline period (r = -0.04, p = 0.72), nor between adherence after the ECT and asthma control at the end of the follow up period (r = -0.02, p = 0.85). During the study there were no significant differences in asthma control between the children with or without EIB (data not shown).

DISCUSSION

We studied the influence of discussing an ECT result with parents on adherence to inhaled maintenance medication, in young children with asthma. We found no clinically relevant change in adherence after the ECT in children, irrespective of the presence of EIB and their baseline adherence. The median baseline adherence was high (83%) and similar in children with or without EIB. Medication beliefs of most parents (82.1%) reflected perceptions about necessity of ICS that outweighed their concerns about ICS. Medication beliefs showed a significant, but not clinically

relevant, positive change after the ECT. Adherence was not related to illness perceptions, medication beliefs or asthma control.

To our knowledge, this is the first prospective intervention study investigating the effects of discussing an ECT result on adherence and parental illness perceptions and medication beliefs in asthmatic children. Our clinical impression was that when ECT results are discussed with parents they can become more aware of these symptoms, and start to realize their child's limitations in play and sports. Two previous studies described a positive effect of lung function monitoring on adherence or asthma control.

Oei et al. [23] showed that monitoring of lung function tests every three months during one year, even without discussing the results, improved asthma control in asthmatic patients aged 14–70 years. They suggested this was due to better adherence, based on their questionnaires. Feldman et al. found a higher, electronically measured, adherence in a group of ethnic minority asthmatic children who received daily feedback on peak expiratory flow monitoring. Baseline adherence in this study group was around 60% [22]. Two reasons may explain the discrepancy between ours and previous studies. First of all, our high baseline adherence (83%) compared to that of Feldman et al. probably precluded an improvement in adherence after feedback on the ECT. Another reason could be the repetition of feedback on lung function tests which may be more effective than a single feedback intervention, as we did. We speculate discussing test results can only induce an increase in adherence in children with intentional non-adherence which is unusual in children enrolled in a comprehensive asthma care program. Potentially, our baseline adherence was high because of the Hawthorne effect, which leads to a transient increased adherence due to participation in a trial, which declines over time.

Most parents (82.1%) showed a positive necessity–concern ratio at baseline as measured with the BMQ. Parents showed a small, but statistical significant change in the necessity–concern ratio, which we interpreted as clinically not relevant. The change in their medication beliefs and illness perceptions was towards increased necessity beliefs and increased understanding of asthma after the ECT. Probably, our comprehensive asthma care program with regular visits to alternately the pediatrician and the nurse practitioner already convinced most parents of the daily use of ICS. This was reflected in a high adherence and many parents with a positive necessity–concern ratio as measured with the BMQ.

We observed similar scores of B-IPQ and BMQ items in children with a high and low adherence. This, together with the observation that children in our study with a low adherence did not improve, suggests that they experienced barriers to improvement that are difficult to influence by discussing ECT results (unintentional non-adherence). This is in line with the results of Klok et al. who showed that in a study population with a high adherence, especially family related barriers are the cause of unintentional non-adherence, for example child raising issues or missing family routines [24].

Previous literature is inconsistent about the relationship between educational level of parents and adherence [4,16]. We found no significant relation between these two, which may be due to the average high level of education in the Netherlands.

Limitations and strengths

The main strengths of our study include the objective, validated, quantitative assessment of adherence in a homogenous group of asthmatic children. Also, all tests were performed and immediately discussed by the same investigator.
A limitation of our study is performing spirometry and ECT's in young children. However, the investigator was very experienced in performing spirometry and ECT's in this age group. The study protocol was designed and validated in our study center [9].
In retrospect, our study group had a high baseline adherence probably due to our comprehensive asthma care program. However, children with a lower adherence did not show an improvement in adherence either. Our results cannot be extrapolated to asthmatic children who are not in a comprehensive asthma care program, as these children probably have a higher intentional non-adherence. The unavoidable drawback of an initially adherence-improving effect of participating in a study may have influenced our findings, however because this effect was also present in children without EIB, we still can conclude that the ECT did not influence adherence.
Future research should be directed to investigate the effect of discussing ECT results with parents of children with a high intentional non-adherence, as can be found in newly referred patients who are not in a comprehensive asthma care program.

Conclusions

We conclude that discussing ECT results with parents does not influence adherence to inhaled maintenance medication in young asthmatic children who are followed up in a comprehensive asthma care program, even when these children have poor baseline adherence. The most likely explanation is that these programs are associated with low intentional non-adherence rates.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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Chapter 3

Emphasizing of shaking the inhaler as part of inhalation instruction is important in young asthmatic children

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ABSTRACT

Background
Current guidelines recommend to monitor inhalation technique in asthmatic children every 3-6 months. The aim of this study was to investigate inhalation technique 6 weeks after instruction in young asthmatic children, using a pressurized metered dose inhaler with spacer.

Methods
91 asthmatic children, 4-8 years, from our outpatient clinic, demonstrated their inhalation technique with a pressurized metered dose inhaler with spacer. Errors in inhalation technique were scored on an inhaler specific standardized checklist designed by the Dutch Lung Foundation. Afterwards, feedback on inhalation technique was provided to the child and his/her parent(s). Six weeks later their inhalation technique was re-evaluated.

Results
Significantly more children carried out a perfect inhalation technique (67.0% vs. 36.3%, p=<0.001) and significantly less children showed one, two or three errors (31.5% vs. 63.7% p=<0.001) 6 weeks after instruction. Significantly more children failed to shake their inhaler 6 weeks after instruction (16.9% vs. 6.6%, p=0.035).

Conclusion
Although we observed a significant improvement in inhalation technique six weeks after instruction with tailored feedback, more young asthmatic children failed to shake their inhaler. We recommend that reinforcement on essential steps that are performed correctly should be highly emphasized

INTRODUCTION

Asthma is the most common chronic illness among children and is featured by inflammation of the lower airways [1]. Inhaled corticosteroids are the cornerstone of treatment for persistent childhood asthma due to their potent anti-inflammatory effects and are recommended for daily use [2]. Correct use of inhalation devices is a prerequisite for successful drug treatment of asthma. Unfortunately inhaler technique is inadequate in many asthmatic children as well as medication adherence in general (50-60%) [3,4]. Even after inhalation instruction many children use their inhaler devices too poorly to result in reliable drug delivery [5,6].
Kamps et al. showed in newly referred asthmatic children, that a single inhalation instruction session is insufficient to maintain appropriate use of daily used inhaled medication, and recommended to repeat instruction at every clinical follow-up [5]. Current international guidelines recommend repeated comprehensive inhalation instructions every 3-6 months to improve inhalation technique [5,7,8]. However, the sustained effect over time of a single inhalation instruction on inhaler technique in young children (4-8 years) using a pressurized metered dose inhaler in conjunction with a spacer (pMDI/s) is not known.
The aim of this study was to investigate inhalation technique 6 weeks after a single instruction in young asthmatic children who are regularly reviewed by a pediatrician, using a pMDI/s.

METHODS AND MATERIALS

Patients

From October 2012 till March 2013, 91 children (aged 4-8 years) with a doctor's diagnosis of asthma and a prescription of inhalation corticosteroids were recruited from the outpatient clinic of the paediatric departments of three hospitals (Medisch Spectrum Twente, Enschede (MST) and Ziekenhuisgroep Twente (ZGT), Hengelo and Almelo). Subjects were enrolled in our standard asthma care program which includes instruction of inhalation technique twice a year i.e. a demonstration of the child's inhalation technique with feedback on the specific items as mentioned in the checklist in Table 1. They were included to participate in the IMPACT study (NL 40615.044.12) to assess the impact of a discussed exercise challenge test on adherence and medication beliefs of parents. Adherence was electronically measured for six weeks before and after the discussed exercise challenge test.

Study design

Children and parents were asked to show their habitual inhalation technique with a pMDI/s i.e. with or without parental supervision to simulate real-life inhalation technique. The majority of the children were helped or supervised by their parents during inhalation in the home situation. These parents were asked to do so during the demonstration as well.
Errors in inhalation technique were scored by the investigator on an inhaler specific standardized checklist designed by the Dutch Lung Foundation [5]. Inhalation technique was demonstrated and scored by 8 items of which 5 were considered to be essential for reliable drug delivery (Table 1). Items were scored as correct or not

Table 1: Inhaler checklist for pMDI/s with number (%) of children making errors at baseline and follow-up.

	Baseline (N=91)	**Follow-up (N=89)**
1 Shake the inhaler*	6 (6.6%)	15 (16.9%)
2 Correct assembly of the spacer device and MDI*	0 (0%)	0 (0%)
3 Sit or stand upright	24 (26.4%)	1 (1.1%)
4 Place mouthpiece between teeth and lips/ facemask over nose and mouth and form a seal*	2 (2.2%)	0 (0%)
5 Hold the spacer in a horizontal position	42 (46.2%)	13 (14.6%)
6 Activation of the canister*	0 (0.0%)	0 (0%)
7 Inhale at least five times	8 (8.8%)	7 (7.9%)
8 Check that spacer valve is moving*	0 (0%)	0 (0%)
* Essential steps		

Note that a child can make more than one error.

correct (error). Immediately afterwards the investigator reviewed the technique with the child and his/her parent(s) and a tailored instruction of approximately 5 minutes was provided. Six weeks later their inhalation technique was demonstrated and scored again by the same investigator using the same checklist.

Questionnaire

Asthma control was assessed before the first inhaler technique demonstration by the Childhood Asthma Control Test (C-ACT, total score 3 – 27) [9]. The C-ACT is especially designed to measure asthma control in asthmatic children 4-11 years old and consists of 7 questions; 4 questions for the child (scores 0-3) and 3 for their parents (scores 1-5). Scores of all questions were summed (range 3-27) and a C-ACT score of ≤19 indicates poor asthma control.

Statistical analyses

Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, depending upon the normality of the data. Categorical variables were expressed as numbers with corresponding proportions.

The percentage of children demonstrating errors before and 6 weeks after instruction was analyzed with a McNemar test.

The association between age or asthma control and inhalation technique was analyzed by a chi square test (categorical variables) or Kruskall Wallis test (not nor-

Table 2: Baseline characteristics

Number of children	91
Median age, years	5.8 (5.4-6.8)
Gender, boys	51 (56%)
Disease duration (years)	1.8 (0.4-3.2)
Maintenance medication	
- fluticasone	72 (79.1%)
- beclomethasone	11 (12.1%)
- salmeterol+fluticasone	8 (8.8%)
C-ACT ≤ 19	15 (16.5%)
C-ACT score	22.2 ± 2.8
Data expressed as mean values ± standard deviation, median (interquartile ranges) or numbers (percentage). Disease duration: years of pediatrician care, C-ACT = Childhood-Asthma Control Test: a score ≤19 indicates uncontrolled asthma [9].	

mally distributed continuous variables). A 2 sided value of $P<0.05$ was considered statistically significant. All analyses were performed using SPSS for Windows, version 20.0.

ETHICAL CONSIDERATIONS

This study was approved by the hospital ethics review board. All parents provided written informed consent to participate in this study.

RESULTS

Ninety-one children of whom 51 boys, 4-8 years of age, were asked to demonstrate their inhalation technique with their metered dose inhaler. Eighty-eight children had only used a pMDI/s before the study; three children had switched within a year prior to the study from a pMDI/s to a breath actuated inhaler. In the context of the IMPACT study these children were reverted to a pMDI/s. All children and parents had been given inhalation instructions at the time of prescription. Table 2 summarizes all baseline characteristics.
Two children were lost during follow up, one patient due to illness, and one patient due to a long travel time to the hospital due to moving house.

Table 3: Number of errors at baseline and follow up (N, %).

		Number of errors at follow up (N, %)					Total
		0	**1**	**2**	**3**	**Missing**	
Numbers of errors at baseline	0	23 (25.3)	9 (9.9)	1 (1.1)	0	0	33 (36.3)
	1	27 (29.7)	8 (8.8)	0	0	2 (2.2)	37 (40.6)
	2	9 (9.9)	4 (4.4)	4 (4.4)	1 (1.1)	0	18 (19.8)
	3	2 (2.2)	0	1 (1.1)	0	0	3 (3.3)
Total		61 (67.0)	21 (23.1)	6 (6.6)	1 (1.1)	2 (2.2)	91 (100)

Table 4: Number of children making essential errors at baseline and follow up.

		Follow up		Total
		No errors	**Errors**	
Baseline	No errors	69	12	81
	Errors	5	3	8
Total		74	15	89

All errors

Table 1 shows every step of the inhaler checklist with errors at baseline and follow up of our population. Table 3 shows the number of errors at baseline and follow up. Of the 91 children 33 (36.3%) carried out all steps correctly at baseline and 61 (67.0%) at follow up ($p<0.01$). At baseline the most common mistake (46.2%) was not holding the spacer in a horizontal position, while at follow up the most common mistake was failing to shake the inhaler (16.9%).

Essential errors

At baseline, eight children made at least one essential error (8.8% of the total patient group). Six of these eight children failed to shake their inhaler, while two did not place the facemask correctly over their nose and mouth (Table 1). At follow up, fifteen children made at least one essential error (16.9%). All these children failed to shake their inhaler. Three children persistently did not shake their inhaler, so there were 12 new children who failed to shake their inhaler at follow up. The increase in the number of children making at least one essential error was not significant ($p=0.14$, Table 4), however the increase in the number of children who failed to shake their inhaler was significant ($p=0.04$).

Age and asthma control

There was no association between age (p=0.79) or asthma control as measured with the C-ACT (p=0.46) and number of errors in inhalation technique.

DISCUSSION

The results of this study demonstrate that 6 weeks after a single inhalation instruction significantly more children (67.7% vs. 36.3%) carried out a perfect inhalation technique. However, of those who did not perform a perfect technique significantly more children made an essential error, with failing to shake their inhaler being the main error (6.6% at baseline, 16.9% six weeks after the single instruction).

We are not aware of any studies investigating the short term effect (6 weeks) of a single inhalation instruction on inhalation technique in outpatient asthmatic children. Kamps et al. showed in a similar study that with at least two consecutive instructions in a 4 week period 93% of children carried out all essential steps correctly when reviewed 6 weeks after the last instruction [5]. However, in daily clinical practice this seems to be too great a burden for patients and health care resources. Focusing on essential errors, we found 6 weeks after instruction already a decline of 91% to 83% of children who carried out all essential steps (i.e. shake the inhaler) correctly. Although, our inhalation instruction regarding not shaking the inhaler was effective in half of the children (3/6), we found twelve new children failing to shake their inhaler at follow up.

Guidelines recommend to monitor inhalation technique in asthmatic children every 3-6 months [8]. According to our observations this interval is too long to prevent the appearance of new essential errors.

Deerojanawong et al. studied outpatient children of the same age using a pMDI/s and observed a perfect inhalation technique in 47.1%. However, they used the checklist based on the recommendations of the National Institute of Health (NIH) which does not incorporates body posture [10]. Excluding the body posture error in our study group we found the same amount of children (46.2%) demonstrating a perfect inhalation technique. Hagmolen of ten Have et al. found 49% of the children demonstrating a perfect inhalation technique using the same checklist of the Dutch Lung Foundation as we did. They studied outpatient asthmatic children with a mean age of 10.5 years old, suggesting better inhalation technique in older aged children [11].

Children in our study showed few essential errors in inhalation technique at baseline (8.8%) compared to 16-40% in other studies among outpatient children using a pMDI/s [5,10,12]. In line with other studies, we observed that failing to shake the inhaler was the most frequent essential error at baseline (6.6%). In the studies of Kamps at al. 19.6% of clinical outpatients and 29% of newly referred children failed to shake their inhaler [5,12]. Not shaking the inhaler reduces the output of the pMDI/s with approximately 35% [13].

Deerojanawong et al. showed a high percentage of essential errors (39.2%) compared to our study but used the NIH checklist that classifies the step of taking 5-6 deep and slow breaths as essential [10]. When using the NIH checklist in our study population, 17.6% showed an essential error at baseline.

We showed no association between asthma control as measured with the C-ACT

and number of errors in inhalation technique. Previous studies are not conclusive about the relation between asthma control and errors in inhalation technique. Most of these studies measured asthma control with clinical study end-points in contrast to the C-ACT used in our study. Probably this discrepancy is also caused by differences in study population and adherence [2,11,12,14].

We hypothesize that the low number of essential errors in our study group compared to other studies is a consequence of the organization of our asthma care. In our clinic, comprehensive asthma management consists of frequent follow up visits every 4 months alternately to a pediatrician and a dedicated asthma nurse who extensively checks inhalation technique.

We were surprised to find more children failing to shake their inhaler 6 weeks after inhalation instruction. This shows that reinforcement of essential steps which previously were performed correctly should be emphasized. When the investigator confronted children and parents with this essential error, they responded they did shake their inhaler at home.

The main strengths of our study include the homogenous group of young asthmatic children using the same device in a narrow age range. The same investigator evaluated all children.

A limitation of our study is that demonstrated inhalation technique observed by parents and health care professionals may not correspond well with inhalation technique in daily life. Although we provided each patient with a structured feedback about their inhalation technique, an investigator bias may have been introduced in these discussions as in any patient-doctor contact.

Furthermore, inhalation technique may have improved due to the use of electronic loggers during the IMPACT study. However, subjects were aware that the loggers could measure adherence, but not inhalation technique.

Further studies could investigate the effect of monitoring the inhalation technique of asthmatic children with modern internet technology, visualizing inhalation technique at home.

Although we observed a significant improvement in perfect inhalation technique six weeks after instruction with tailored feedback, more young asthmatic children failed to shake their inhaler. We recommend that reinforcement on essential steps that are performed correctly should be highly emphasized.

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Chapter 4

Reversibility after inhaling salbutamol in different body postures in asthmatic children: a pilot study

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SUMMARY

Rationale
Pulmonary medication is mostly delivered in the form of medical aerosols to minimize systemic side effects. A major drawback of inhaled medication is that the majority of inhaled particles impacts in the oropharynx at the sharp bend of the airway. Stretching the airway by a forward leaning body posture with the neck extended ("sniffing position") may improve pulmonary deposition and clinical effects.

Methods
41 asthmatic children who were planned for standard reversibility testing at the pulmonary function lab, alternately inhaled 200µg salbutamol with an Autohaler® in the standard or in the forward leaning body posture. Forced Expiratory Volume in 1 s (FEV_1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), Mean Expiratory Flow at 25% of vital capacity (MEF_{25}) and Mean Expiratory Flow at 75% of vital capacity (MEF_{75}) were analysed.

Results
The children in the forward leaning body posture group showed a significantly higher mean FEV_1 reversibility than the control group after inhalation of 200 µg salbutamol (10.2% versus 4.1%, p = 0.019). Additionally, mean MEF_{75} was significantly more reversible in the forward leaning body posture group versus the standard body posture group (32.2% resp. 8.9%, = 0.013).

Conclusion
This pilot study showed a higher reversibility of FEV_1 and MEF_{75} after inhaling salbutamol in a forward leaning body posture compared to the standard body posture in asthmatic children. This suggests that pulmonary effects of salbutamol can be improved by inhaling in a forward leaning body posture with the neck extended. This effect is possibly due to a higher pulmonary deposition of salbutamol and should be confirmed in a randomized controlled trial.

INTRODUCTION

Inhaled bronchodilators are recommended as rescue medication for all children with asthma [1]. Deposition of inhaled medication in the upper airway can compromise deposition at the target area. This upper airway deposition is caused by the sharp angle between the pharynx and trachea [2,3]. In asthmatic children the loss of inhaled medication may even be greater as the upper airway is smaller and has a different geometry. Even with optimal inhalation via a breath actuated inhaler (BAI) 50–60% of the dose of beclomethasone diproprionate impacted in the oropharynx in children under the age of 12, as measured in a radio-labelling study [4]. In daily practice the inhalation technique is frequently less optimal leading to an even higher loss of medication [5].
Brandao et al. showed that inhaling nebulised bronchodilators in a forward leaning body posture during an asthma exacerbation in asthmatic young adults, led to a faster recovery of lung function compared to the conventional body posture [6]. They suggested that this could be caused by a higher pulmonary deposition of the nebulised medication in the forward leaning posture.
We hypothesized that stretching the bend in the upper airway during inhalation could improve the effect of salbutamol on lung function.
The aim of this study was to compare the reversibility of lung function in asthmatic children after a dose of 200µg salbutamol that was inhaled either in the forward leaning body posture with the neck extended, or in the standard body posture.

MATERIALS AND METHODS

Patients

Clinically stable patients aged 6 to 16 years old, with pediatrician diagnosed mild to moderate asthma, who underwent a planned spirometry in Medisch Spectrum Twente, Enschede from May to August 2013, participated in this prospective pilot study. Children were not allowed to use long acting bronchodilators 24 h before testing, or short acting bronchodilators 8 h before testing.
The medical ethical committee reviewed our study protocol and declared that our study did not meet the criteria necessary for an assessment by a medical ethical committee according to the Dutch law, because the children were not subjected to procedures deviating from the normal procedures. All children and parents received verbal information and their participation was voluntarily.

Pulmonary function measurements

Spirometry was performed by standard pulmonary function tests before and after the administration of 200µg salbutamol, administered with an Autohaler®. All pulmonary function measurements – Forced Expiratory Volume in 1 s (FEV_1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), Mean Expiratory Flow at 25% of vital capacity (MEF_{25}) and Mean Expiratory Flow at 75% of vital capacity (MEF_{75}) – were performed in the same standard upright body posture. Percentage of predicted baseline FEV_1 was measured with the aid of the Koopman formulas [7]. Reversibility was calculated as follows: (value after salbutamol – value at baseline)/value at baseline [8]. All spirometry measurements consisted of duplicated

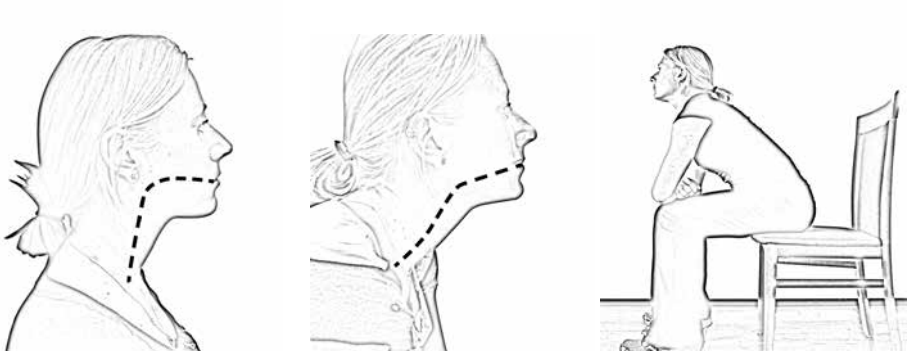

Figure 1 Standard and forward leaning body posture. 90° bent airway in standard body posture (left); stretched airway in forward leaning body posture with the neck extended ("sniffing" position) (middle); forward leaning posture (right).

full flow volume loops, using standard ERS protocol [9]. The best values for all variables were used for analysis. Visual incentives such as blowing out candles or knocking down bowling pins were used to optimize spirometric effort.

Inhalation technique

Patients inhaled alternately in the standard upright body posture described on the standardized checklists designed by the Dutch Asthma Foundation [10] or in the alternative body posture: a forward leaning body posture with the neck extended (Fig. 1).

The inhaled medication was administered to all children by the same investigator who did not perform the pulmonary function measurements. The pulmonary function technician was not blinded to the body posture during inhalation.

Sample size calculation

No sample size calculation was performed, because this study was deemed a pilot study. This study was conducted between May 2013 and August 2013 (12 weeks). Results were analysed after the inclusion of 41 children.

Statistical analyses

Data was expressed as mean values ± standard deviation (SD), and 95% confidence intervals (95CI), where appropriate, for normally distributed data, as median (Inter Quartile Range; IQR 25-75th) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal. Continuous variables were visualised with histograms. When applicable, between-group comparison of continuous, normally distributed data was performed using a t-test. In the case of not normally distributed data a Mann–Whitney U test was performed. Between-group comparison of nominal or ordinal variables was performed by Chi-square tests.

Best values of spirometry measurements were used for statistical calculations. Data was analyzed with SPSS® for Windows® version 15 (IBM, Chicago, IL, USA) analytical software. A two-sided value of $P < 0.05$ was considered statistically significant.

Table 1: Baseline characteristics subdivided on body posture during inhalation.

	Standard	Forward leaning
Number of patients	20	21
Age, years	9.0 (7.4-11.7)	12.4 (8.3-13.8)
Boys	9 (45%)	12 (57%)
First spirometry	10 (50%)	6 (29%)
FEV_1 baseline (mean % of predicted)	94.2% ± 13.5%	86.3% ± 15.5%
Exacerbation <6 months prior to study	2 (10%)	2 (10%)
Maintenance medication	20 (100%)	17 (81%)

Data expressed as mean ± SD, median (IQR) or numbers (percentage).
FEV_1: forced expiratory volume in 1 s, percentage of predicted based on the reference values of Koopman et al. [7].
Exacerbation was defined as hospital admission or use of systemic corticosteroids.

Table 2: Change in pulmonary function after inhaling 200µg salbutamol in different body postures.

	Standard body posture	Forward leaning body posture	Difference (95%CI)	P value
FEV_1 reversibility	4.1 (7.4)	10.2 (8.5)	–0.111; –0.011	0.019
VC reversibility	0.8 (3.9)	2.2 (3.9)	–0.039; 0.010	0.241
PEF reversibility	9.4 (14.7)	11.1 (16.3)	–0.116; 0.083	0.740
MEF_{25} reversibility	9.9 (15.2)	18.3 (24.0)	–0.212; 0.045	0.194
MEF_{75} reversibility	8.9 (30.5)	32.2 (25.8)	–0.414; –0.052	0.013

Data expressed as mean ± SD.
FEV_1: Forced Expiratory Volume in 1 s, FVC: Forced Vital Capacity, PEF: Peak Expiratory Flow, MEF_{25}: Mean Expiratory Flow at 25% of vital capacity, MEF_{75}: Mean Expiratory Flow at 75% of vital capacity.

RESULTS

Forty-one consecutive children, 6-16 years of age, 21 boys, participated in the study, none were excluded. Baseline characteristics did not significantly differ between the two body postures groups. There was a trend towards a younger median age ($p = 0.109$), a better baseline FEV_1 ($p = 0.091$, 95CI -1.3; 17.1) and a greater proportion of newly referred patients ($p = 0.160$) in the standard body posture group. Table 1 summarizes the baseline characteristics of the two groups subdivided on body posture during inhalation.

Spirometry

The children in the forward leaning body posture group showed a 10.2% reversibility in FEV_1 after inhalation of 200µg salbutamol, while in the standard body posture group this was 4.1% ($p = 0.019$). Mean MEF_{75} reversibility was 32.2%

in the forward leaning group versus 8.9% in the standard body posture group ($p = 0.013$). Reversibility in VC, PEF and MEF_{25} was numerically, but not significantly, higher in the forward leaning group as well (see Table 2).

DISCUSSION

This pilot study indicates a significantly higher reversibility of lung function expressed as FEV_1 and MEF_{75} if 200µg salbutamol is inhaled in a forward leaning body posture, compared to the standard body posture in asthmatic children. These results suggest that a forward leaning body posture can improve pulmonary effects of salbutamol, probably by a higher pulmonary deposition.
To our knowledge, this is the first study investigating the effect of a forward leaning body posture compared to the standard body posture during inhalation of salbutamol on lung function reversibility in clinically stable asthmatic children.
Our findings are in line with the study of Brandao et al. that showed a greater clinical effect of a forward leaning body posture compared to the conventional body posture during the inhalation of nebulised bronchodilators in young adults during an asthma exacerbation [6]. They suggested this difference was due to a higher pulmonary deposition of inhaled medication in the forward leaning body posture.
The significant higher reversibility of the FEV_1 and MEF_{75} and not of the PEF, VC and MEF_{25} in the forward leaning body posture, as observed in our study, suggests mainly the conductive airways profited of the different body posture. A potential limitation of this pilot study was the way we included the children into the study. Children were alternately included in the standard or the forward leaning body posture group, in order to exclude selection bias. However, there was an imbalance in experience with spirometry and baseline FEV_1: 50% of the children in the standard body posture group performed their first spirometry versus 29% in the forward leaning group. The difference was not significant and all children performed technically appropriate spirometries. In contrast to a significant difference in reversibility of MEF_{75} and FEV_1, no significant difference in reversibility of PEF between the groups was observed, suggesting technique of performing spirometry was comparable between groups. An additional limitation was that the pulmonary function technician was not blinded to body posture during inhalation. These limitations could have resulted in bias, however, we regard the observed differences as clinically relevant.
We purposely chose a low dose of salbutamol so as to be on the steep slope of the dose response curve. Perhaps higher doses such as 400µg or 800µg salbutamol could be used to discover the top of the dose response curve.
Our observation suggests that inhaling in a forward leaning body posture improves medication delivery to the lower airways. A higher pulmonary deposition of inhaled medication may lead to a reduction in dose and consequently a reduction in side effects, especially when inhaling corticosteroids. Dubus et al. showed that approximately 60% of asthmatic children using beclomethasone diproprionate or budesonide reported local side effects such as coughing, hoarseness, dysphonia and oral candidiasis [11].
In the future, the effect of a forward leaning body posture during inhalation in

asthmatic children should be assessed in a randomized controlled trial with different doses of salbutamol, preferably radio-labeled. Less impaction of inhaled medication in the upper airway may be more relevant for other medication than bronchodilators, such as corticosteroids and antibiotics.

CONCLUSION

This pilot study showed a higher reversibility of FEV_1 and MEF_{75} after inhaling salbutamol in a forward leaning body posture compared to the standard body posture in asthmatic children. This suggests that pulmonary effects of salbutamol can be improved by inhaling in a forward leaning body posture with the neck extended, possibly due to a higher pulmonary deposition of salbutamol.

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Chapter 5

Reversibility of pulmonary function after inhaling salbutamol in different doses and body postures in asthmatic children

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ABSTRACT

Rationale
Pulmonary medication is often delivered in the form of medical aerosols designed for inhalation. Recently, breath actuated inhalers (BAI's) gained popularity as they can be used without spacers. A major drawback of BAI's is the impaction in the upper airway. Stretching the upper airway by a forward leaning body posture with the neck extended ("sniffing position") during inhalation may reduce upper airway impaction and improve pulmonary deposition. Aim of this study was to investigate the reversibility of lung function with different doses salbutamol inhaled with a BAI in the forward leaning posture compared to the standard posture in asthmatic children.

Methods
22 clinically stable asthmatic children, 5-14 years old, performed four reversibility measurements. Children inhaled 200µg or 400µg salbutamol with a BAI in the standard or in the forward leaning posture with the neck extended in a prospective randomized single-blinded cross-over design.

Results
Reversibility of lung function after inhaling salbutamol in the forward leaning posture was not significantly different compared to inhalation in the standard posture. Mean FEV_1 reversibility was significantly greater after inhaling 400µg salbutamol compared to 200µg salbutamol in the standard posture (9.4% ± 9.5% versus 4.5% ± 7.5%, difference 4.9% (95CI 0.9; 9.0%); p = 0.021).

Conclusion
In clinically stable asthmatic children, inhalation of salbutamol with a BAI in a forward leaning posture does not increase reversibility of lung function. Inhalation of 400µg compared to 200µg salbutamol with a BAI does improve reversibility.

INTRODUCTION

For all patients with asthma, inhaled medication is recommended [1]. Deposition at the target area however is compromized by impaction of inhaled medication in the upper airway, which is compounded by the sharp angle between the pharynx and trachea [2,3]. In children the loss of inhaled medication is probably even greater as the upper airway is smaller which increases flow rate. To reduce impaction spacers were introduced, however breath actuated inhalers (BAI's), which can be used without spacers, have gained popularity. BAI's are easy to use and frequently administered as bronchodilators for measuring reversibility of pulmonary function in children. Potential drawback of BAI's compared to metered-dose inhalers in conjunction with spacers (MDI/s) is the loss of medication in the upper airway [3,4]. In a radio-labeled study in asthmatic children under the age of twelve, 50–60% of the inhaled dose of a BAI impacted in the oropharynx [4]. In contrast, inhaling from a MDI/s resulted in only 30% impaction in the oropharynx in asthmatic adults [3].
Brandao et al. showed that inhaling nebulized bronchodilators in a forward leaning posture during an asthma exacerbation in asthmatic adults, led to a faster recovery of lung function compared to inhaling in the standard body posture [5]. It was suggested that this was due to a higher pulmonary deposition of the nebulized medication by inhaling in the forward leaning posture [5]. Indeed a forward leaning posture stretches the upper airway which may reduce the loss of inhaled medication in the upper airway [5,7].
Our previous pilot study showed a higher reversibility of FEV_1 and MEF_{75} after inhaling salbutamol in a forward leaning body posture in asthmatic children, suggesting that bronchodilatory effects of salbutamol can be improved by changing body posture during inhalation [8].
Aim of this study is to compare the reversibility of lung function when inhaling 200µg and 400µg salbutamol with a BAI in the forward leaning posture or in the standard posture in asthmatic children.

METHODS

Patients

Children aged 5 till 14 years old, with a pediatrician diagnosis of mild to moderate asthma, were recruited from the outpatient clinic of the pediatric department of Medisch Spectrum Twente, Enschede, The Netherlands. They participated in this prospective randomized single-blinded, cross-over study. Children were not allowed to use long acting bronchodilators 24 h before testing, short acting bronchodilators 8 h before testing or leukotriene antagonists 24 h before testing. Children with an asthma exacerbation in the last 4 weeks prior to the study (e.g. hospital admission or use of systemic corticosteroids) were excluded.

Ethical considerations

This study was approved by the Ethics Review Board Twente. All children and parents/guardians received written patient information and provided written informed consent to participate in this study.

Pulmonary function measurements

All pulmonary function measurements were performed by the same physician investigator from the pediatric department with an extensive training and experience with spirometry in children. A MicroLoop® spirometer, in combination with Spida5® software, was used to measure pulmonary volumes and flow-volume loops. Spirometry was performed by standard pulmonary function measurements before and 10 min after the inhalation of 200µg or 400µg salbutamol [9]. Although body postures whilst inhaling salbutamol were different, all pulmonary function measurements were performed in the same standard upright body posture. All children performed four spirometry pulmonary function measurements within a period of maximal two weeks. The minimum washout period was 24 h, the maximum was 7 days. The spirometry measurements were planned within 2 h on the different days because of the possible pulmonary function variations during the day. Variables FEV_1, VC, PEF, MEF_{25} and MEF_{75} were measured as well as the Mean Inspiratory Flow at 50% of vital capacity (MIF_{50}) and Forced Inspiratory Vital Capacity (FIVC) if applicable. The best values for all variables were used for analysis. Percentage of predicted baseline FEV_1 was measured with the aid of the Koopman formulas [10]. Reversibility was measured with the formula recommended in the ERS-ATS 2005 lung function interpretation document namely the percent change from baseline; in formula: (variable after salbutamol - variable at baseline)/variable at baseline [11]. All parameters were obtained from series of at least three reliable forced expiratory curves [9]. The best values of FEV_1, FVC and PEF were recorded after examining all usable curves, even if they did not came from the same curve [9]. For the parameters MEF_{25} and the MEF_{75} we recorded the best value from a curve with a FVC that was within 95% of the highest FVC. Children with a difference of $\geq$ 12% in absolute FEV_1 pre-salbutamol between measurements were excluded for the relevant sub-analyzes.

Visual incentives such as blowing out candles or knocking down bowling pins were used to optimize spirometric technique.

Body postures during inhalation

To measure reversibility of lung function during the spirometry assessment, children inhaled the same standard dose of either 200µg or 400µg salbutamol (Airomir™) with an autohaler® in a randomized order. The children inhaled both doses of salbutamol in the standard body posture as pointed out on the standardized checklists designed by the Dutch Asthma Foundation [12] as well as in the forward leaning body posture as pointed out on Figs. 1-3 in a randomized order and a single-blinded design. The study scheme is illustrated in Fig. 4. For randomization block sizes of 2 and 4 children were used with the aid of a computerized randomization method performed by an independent assistant.

All children received the medication by the investigator who was not involved in the pulmonary function measurements. The investigator who performed the pulmonary function measurements was ignorant of dose and body posture during inhalation of salbutamol. Ten minutes after the administration of salbutamol spirometry measurements were repeated.

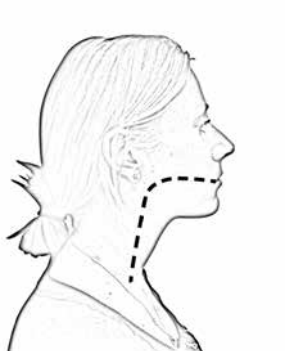

Fig. 1. Curved airway in standard posture.

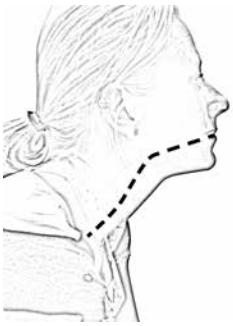

Fig. 2. Stretched airway in forward leaning posture.

Fig. 3. Forward leaning body posture.

Questionnaires

Asthma control was measured with the (Childhood) Asthma Control Test (C-ACT for children ≤ 12 years old, ACT for children > 12 years old). A score ≤19 indicates uncontrolled asthma [13,14]. Possible discomfort in the forward leaning posture and possible side effects of 400µg salbutamol were analyzed with selfdesigned questionnaires.

Sample size calculation

A previous pilot study with a comparable design showed an average reversibility of FEV_1 of 4.1% (SD ± 7.4%) in the control group of asthmatic children who received 200µg salbutamol in the standard posture [8]. The intervention group received 200µg salbutamol in the forward leaning posture and showed an average reversibility in FEV_1 of 10.2% (SD ± 8.5%). To document this significant difference in reversibility of FEV_1 with a McNemar test in the current randomized single-blind cross-over study we did a power calculation. A sample size of 15 achieves 90% power to detect a difference of -6.1 between the null hypothesis mean of 4.1 and the alternative hypothesis mean of 10.2 with a known standard deviation of 8.0 and with a significance (alpha) of 0.050 using a two-sided one-sample t-test. To take possible drop outs into account we included 20 children.

Statistical analysis

Best values of spirometric measurements were used for statistical calculations. Results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (interquartile range) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal. Normality of data was visually inspected. Within person changes in continuous variables (e.g. FEV_1 reversibility) were analyzed with a paired T-test or a Wilcoxon signed rank test, as appropriate. Between group differences (e.g. standard versus forward leaning posture) in continuous variables (e.g. FEV_1 reversibility) were analyzed with independent T-test or a Wilcoxon Rank Sum Test, as appropriate. A possible carry-over or period effect was analyzed with the Hills and Armitage test.

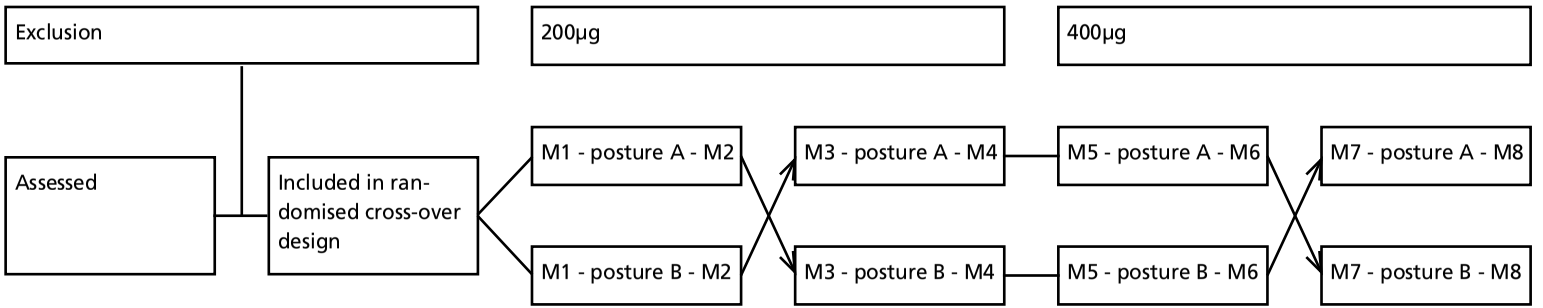

Figure 4. Study scheme
M. spirometry measurement with numbers identifying the first up to the eighth spirometry
posture A: standard body posture
posture B: forward leaning body posture

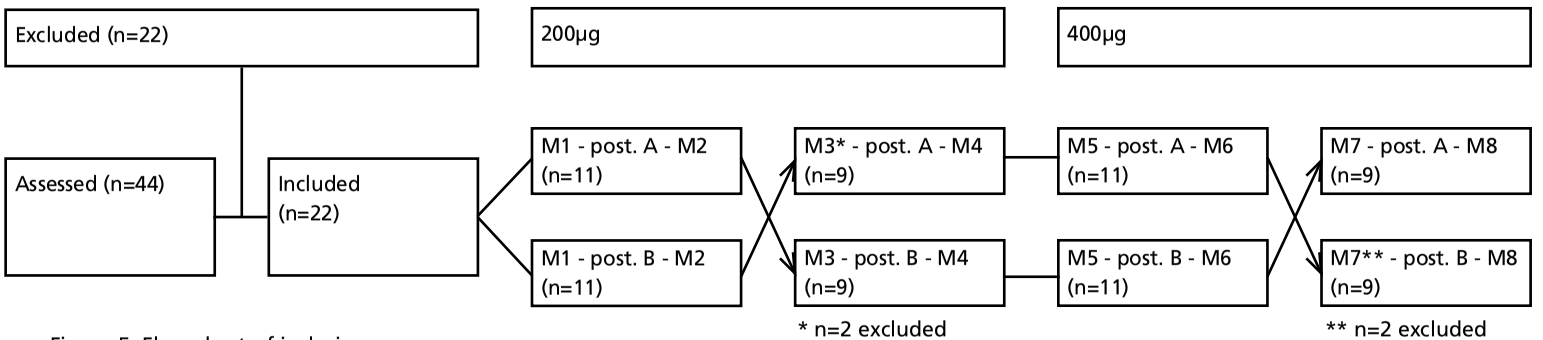

Figure 5. Flow chart of inclusion
M. spirometry measurement with numbers identifying the first up to the eighth spirometry
post. A: standard body posture
post. B: forward leaning body posture

Table 1: Baseline characteristics

Number of patients	20
Age, years (median (IQR))	8.0 (7.0-9.8)
Gender, boys (N (%))	9 (45)
FEV_1 (mean % of predicted ± SD)	86.7 ± 9.8
FVC (mean % of predicted ± SD)	97.4 ± 12.0
Medication (N (%))	
ICS	18 (90)
LTRA's	8 (40
LABA	1 (5)
Antihistaminica (N (%))	8 (40)
Allergy status (N (%))	
- Positive	13 (65)
- Negative	4 (20)
- Unknown	3 (15)
(C-)ACT score (mean ± SD)	21.6 ± 3.1

IQR: interquartile range; FEV_1: forced expiratory volume in 1 s; SD: standard deviation;
ICS = inhaled corticosteroid;
LTRAs = leukotriene receptor antagonists. LABA = long-acting ß2 -agonist;
Positive allergy status = proved by skin prick
test or blood sample; C-ACT = (Childhood-) Asthma Control Test: a score ≤19
indicates uncontrolled asthma [13,14].

Table 2: Spirometry results group 200µg in the standard posture and the forward leaning posture (n = 18).

	Standard posture	Forward leaning posture	Difference (95%CI); p-value
FEV_1 rev (mean%, SD)	6.0 (8.1)	6.0 (8.1)	0.4 (-0.043; 0.034); p = 0.811
FVC rev (mean%, SD)	1.0 (7.7)	2.2 (3.9)	1.2 (-0.054; 0.031); p = 0.574
PEF rev (mean%, SD)	9.1 (11.7)	7.3 (10.3)	1.8 (-0.037; 0.072); p = 0.507
MEF_{25} rev (mean%, SD)	17.1 (23.7)	20.1 (26.6)	3.0 (-0.161; 0.101); p = 0.645
MEF_{75} rev (mean%, SD)	36.5 (66.2)	24.1 (36.1)	12.4 (-0.176; 0.425); p = 0.394

Rev = reversibility.

Data were analyzed with SPSS® for Windows® version 21 (IBM, Chicago, IL, USA) analytical software. A 2 sided value of $P < 0.05$ was considered statistically significant.

RESULTS

Of the forty-four children we approached to participate in this study, twenty-two children were included (Fig. 5). The most common reasons why children/parents did not want to participate in this study were their inability to combine four hospital visits in two weeks with their family activities.
Baseline characteristics of the twenty patients are shown in Table 1.

Table 3: Spirometry results group 400µg in the standard posture and the forward leaning posture (n = 18).

	Standard posture	Forward leaning posture	Difference (95%CI); p-value
FEV_1 rev (mean%, SD)	10.3 (9.6)	10.6 (10.7)	0.3 (-0.027; 0.020); p = 0.772
FVC rev (mean%, SD)	3.4 (4.4)	4.8 (6.2)	1.4 (-0.046; 0.017); p = 0.355
PEF rev (mean%, SD)	12.6 (9.9)	13.4(10.9)	0.8 (-0.056; 0.050); p = 0.787
MEF_{25} rev (mean%, SD)	19.6 (22.9)	24.0 (24.5)	4.4 (-0.132; 0.045); p = 0.309
MEF_{75} rev (mean%, SD)	31.1 (32.4)	32.6 (41.3)	1.5 (-0.157; 0.126); p = 0.802

Rev = reversibility.

No carry-over or period effects were observed. Comparing the children who reliable performed all four measurements (n = 16), mean FEV_1 reversibility was significantly greater after inhaling 400µg salbutamol in the standard posture compared to inhaling 200µg salbutamol in the standard posture (9.4% ± 9.5% versus 4.5% ± 7.5%, difference 4.9% (95CI 0.9; 9.0%); p = 0.021). The same analyzes in the forward leaning posture also showed a significantly greater mean FEV_1 reversibility after inhaling 400µg salbutamol compared to 200µg salbutamol (9.5% ± 10.3% versus 5.9% ± 8.2%, difference 3.6% (95CI 0.4; 6.9%); p = 0.032). The other spirometric parameters in both body postures did not differ significantly (data not shown).

Reversibility in different body postures with 200µg and 400 µg salbutamol
Two children were excluded in this analyzes because of a difference of ≥ 12% in absolute FEV_1 pre-salbutamol between the two measurements. The remaining children (n = 18) in the forward leaning posture did not show a significantly greater mean reversibility for all parameters after inhalation of 200µg compared to the standard posture group (FEV_1 reversibility 6.0 ± 8.1% vs. 5.6 ± 8.3% respectively, p = 0.811). All spirometry results of the two postures groups are shown in Table 2. Two children were excluded in this analyzes because of a difference of ≥ 12% in absolute FEV_1 between the two measurements. The remaining group of children (n = 18) in the forward leaning posture group did not show a significantly greater mean reversibility for all parameters after inhalation of 400µg compared to the standard posture group (FEV_1 reversibility 10.6 ± 10.7% vs. 10.3 ± 9.6% respectively, p = 0.722). All spirometry results of the two postures groups are shown in Table 3.

Questionnaires

Asthma control test
Of the twenty children who participated in this study, two were older than twelve years old. 75% (n = 15) of the children showed a score of 20 points or more indicating controlled asthma. The other 25% (n = 5) of the children showed a score between 13 and 19 points indicating uncontrolled asthma.

Side effects of salbutamol 200µg and 400µg
We compared the side effects of 200 and 400µg salbutamol (palpitations, tremor,

discomfort and rash) with the aid of a selfdesigned questionnaire. 25% (n = 5) of the children complained about side effects after inhalation of 400µg salbutamol. Three children complained about shaky hands, one experienced some headache, and one experienced an itchy skin. None of the twenty children complained about palpitations.

Discomfort in the forward leaning posture
We also analyzed the possible discomfort of inhalation in the forward leaning posture with the aid of a self-designed questionnaire. 50% (n = 10) of the children complained about some discomfort in the forward leaning posture. Six children experienced some discomfort in their neck, three children in their back, one in his elbows and one complained about some difficulty to swallow. For all patients the discomfort was bearable.

DISCUSSION

Inhaling in a forward leaning posture did not increase reversibility of spirometric parameters compared to the standard posture in asthmatic children. Inhalation of 400µg salbutamol with a BAI resulted in a significantly higher reversibility of FEV_1 compared to inhaling 200µg salbutamol.
To our knowledge this is the first study which analyzed the effect of inhalation of salbutamol with a BAI on reversibility of lung function in a forward leaning posture compared to the standard posture in asthmatic children.
Our previous pilot study showed a significantly higher reversibility of FEV_1 and MEF_{75} after inhaling salbutamol in a forward leaning body posture compared to the standard body posture in asthmatic children [8]. Patient selection may have resulted in a different outcome in our current study. Also, the forward leaning group in our pilot study was on average older (12 years) compared to our current study (8 years). We speculate that older children inhale at a higher inspiratory flow increasing the impaction in the upper airway. A forward leaning posture may be of greater importance in this age group. Baseline lung function FEV_1 was comparable between the forward leaning posture group in the pilot study and our current study.
Brandao showed that inhalation of nebulized bronchodilators in a forward leaning posture resulted in a faster FEV_1 recovery in adults during an asthma exacerbation [5]. It was suggested this was due to a higher pulmonary deposition of inhaled medication in the forward leaning posture. Indeed a forward leaning posture stretches the upper airway, and possibly reduces the loss of inhaled medication in the upper airway. We did not find an effect of inhaling in a forward leaning body posture.
A possible reason for the discrepancy between our observations and Brandao's study is that stretching the upper airway may be of greater influence when inhaling large particles as in nebulized bronchodilators compared to small particles as used in a BAI.
Also, Brandao selected adults with an asthma exacerbation in contrast to our study that investigated clinically stable asthmatic children. During an asthma attack there is a different breathing pattern with a tachypnea resulting in higher flow rates in the upper airway, increasing the impaction of particles in the upper

airway. Stretching the upper airway may reduce the increased oropharyngeal impaction of medication during an asthma attack. Another confounder of the study of Brandao may be that patients breathed during nebulization for 10 min in the forward leaning posture, which may on itself have speeded the rate of recovery of lung function as well. Breathing in a forward leaning posture shifts the center of gravity and optimizes expiration [15].

ERS guidelines recommend to administer 400µg salbutamol for measurement of reversibility in children, but do not specify the device employed [9]. In daily clinical practice, there is a great variability of the administered dose of salbutamol as well as the device used. Dosing of inhaled medication with a BAI should be theoretically higher, as impaction of inhaled medication of a BAI seems to be higher compared to a MDI (50–60% vs. 30%), although no reliable measurements were performed in asthmatic children using a MDI [3,4].

We found a significantly greater mean FEV_1 reversibility after inhaling 400µg salbutamol in both body postures. Our results strongly favor administration of 400µg instead of 200µg salbutamol when using a BAI for reversibility measurements.

The main strengths of our study include the single-blinded (i.e. the investigator was blinded to the body posture), crossover, randomized design. Additionally, the same two investigators assisted medication administration and performed spirometric measurements within a period of 2 weeks per child. Limitations include our measurements of only 10 min post bronchodilator, which could have underestimated reversibility. However in daily practice lung function reversibility is commonly measured after 10 min based on the international guidelines of the ATS-ERS taskforce recommendations [9].

A future study could investigate the effect of inhalation of bronchodilators in a BAI or with large particles such as dry powder in a forward leaning posture during an asthma attack in children.

CONCLUSIONS

In clinically stable asthmatic children, inhalation of salbutamol with a BAI in a forward leaning posture does not increase reversibility of lung function. We do recommend to administer 400µg instead of 200µg salbutamol with a BAI in reversibility measurements, since inhalation of 400µg showed significantly greater reversibility compared to inhalation of 200µg salbutamol.

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Chapter 6

The effect of body posture during medication inhalation on exercise induced bronchoconstriction in asthmatic children

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ABSTRACT

Rationale
Inhaling medication in a standard body posture leads to impaction of particles in the sharp angle of the upper airway. Stretching the upper airway by extending the neck in a forward leaning body posture may improve pulmonary deposition. A single dose of inhaled corticosteroids (ICS) offers acute, but moderate protection against exercise induced bronchoconstriction (EIB). This study investigated whether inhaling a single dose of ICS in a forward leaning posture improves this protection against EIB.

Methods
32 Asthmatic children, 5-16 years, with EIB (median fall in FEV_1 or $FEV_{0.5}$ 30.9%) performed two exercise challenge tests (ECT's) with spirometry in a single blinded cross-over trial design. Children inhaled a single dose of 200µg beclomethasone dipropionate (BDP) 4 h before the ECT, once in the standard posture and once with the neck extended in a forward leaning posture. Spirometry was also performed before the inhalation of the single dose of BDP.

Results
Inhalation of BDP in both body postures provided similar protection against EIB (fall in FEV_1 or $FEV_{0.5}$ in standard posture 16.7%; in forward leaning posture 15.1%, $p = 0.83$). Inhaling ICS in a forward leaning posture significantly delayed EIB compared to inhaling in the standard posture (respectively 2.5 min ± 1.0 min vs. 1.6 min ± 0.8 min; difference 0.9 min (95CI 0.25; 1.44 min); $p = 0.01$).

Conclusion
Inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in asthmatic children, but the forward leaning posture resulted in a delay of EIB.

INTRODUCTION

In recent years there is a trend towards the use of breath actuated inhalers (BAI's) to overcome coordination problems. A drawback however is the massive impaction in the oropharynx. A radio-labelled study showed that under optimal conditions in children of 5-14 years 40-60% of the dose of beclomethasone dipropionate (BDP) inhaled via a BAI impacted in the oropharynx. Oropharyngeal deposition was inversely related to age [1]. Dubus et al. showed that approximately 60% of asthmatic children using inhaled BDP or budesonide reported local side effects such as coughing, hoarseness, dysphonia and oral candidiasis [2].
A recent study of Brandao et al. showed that inhaling nebulised bronchodilators in a forward leaning posture during an asthma exacerbation improved recovery of lung function in asthmatic adults compared to the conventional posture [3]. It was suggested that this was due to an increased pulmonary deposition [4,4a,4b].
Exercise induced bronchoconstriction (EIB) is a highly prevalent and specific symptom of childhood asthma and reflects airway inflammation [5]. Long term regular use of inhaled corticosteroids (ICS) reduces EIB in asthmatic children [6]. Several studies showed that a single high dose of ICS (1000-1600µg), also offers acute protection against EIB [7-10]. We hypothesize that a single low dose of 200µg ICS inhaled in a forward leaning body posture with the neck extended would also improve protection against EIB.
The aim of this study was to investigate the protective effect against EIB of a single low dose of 200µg BDP inhaled 4 h prior to an ECT.

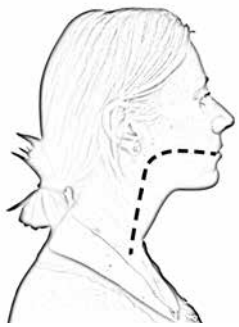
METHODS

Subjects

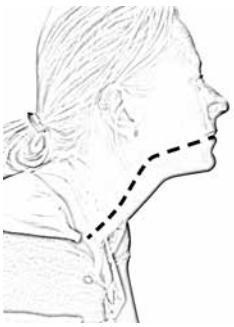
This study had a prospective cross-over design. Children 5-16 years, with a pediatrician's diagnosis of asthma were recruited from the outpatient clinic of the paediatric department of Medisch Spectrum Twente, Enschede, The Netherlands, from October 2013 to February 2014. None were taking ICS or nasal corticosteroids for at least 2 months prior to the study. Children with other pulmonary or cardiac disorders were excluded. Children being admitted to the hospital or being prescribed systemic corticosteroids because of an exacerbation in the last eight weeks prior to the ECT were excluded.

Inhalation technique

Children performed two ECT's within a time period of two weeks preceded by the inhalation of 200µg BDP with an Autohaler® (Qvar®) without a spacer. Four hours prior to one ECT they inhaled BDP in the standard body posture and head position according to the standardized instructions from the Dutch Lung Foundation [11]. Four hours prior to the other ECT they inhaled BDP in the forward leaning body posture with the neck extended (Fig. 1). The different body postures during inhalation were randomized. The investigator performing the ECT was blinded to the body posture in which the children had inhaled their medication.
A well-trained medical student administered the medication at the child's home or school, after a baseline pulmonary function measurement was performed



Curved airway in standard posture



Stretched airway in forward leaning posture

Forward leaning body posture.

Fig. 1. Different body postures during BDP inhalation.

Exercise challenge test

In the hours between the medication administration and the ECT, children were allowed to go to school or play but without exercising. Therefore, parents had to take their child to the ECT by car, while older children arrived by bus or scooter. The two ECT's were performed within a time period of 2 weeks at an indoor ice skating rink, because of the standardized cold and dry air conditions (9.5-10° and humidity 57-59%), reflecting real life outdoor conditions in the Netherlands. The minimal time period between the two ECT's was 48 h.

The ECT's were performed as previously described by Van Leeuwen et al. and Driessen et al. [12,13]. In summary, children 6-10 years old jumped for a maximum of 6 min on a jumping castle and children 12-16 years old performed both ECT's on a treadmill with a 10° slope (Trimline® 7150). Children 10-12 years old could choose between the two ECT formats. Heart rate was continuously monitored by a radiographic device (Garmin Forerunner 610) and the target was to achieve 80-90% of the maximum estimated heart rate (220-age). Pulmonary function was measured before, during and after exercise using standard European Respiratory Society (ERS) protocol [14] in case of an ECT on the jumping castle and only before and after the ECT in case of running on the treadmill. An exercise induced fall in FEV_1 of ≥13% (or $FEV_{0.5}$ if FEV_1 was not reproducible in the youngest children) compared to baseline was considered as positive for EIB [15]. An exercise induced fall in FEV_1 or $FEV_{0.5}$ ≥13% during exercise compared to baseline was considered positive for breakthrough asthma. Percentage of predicted baseline FEV_1 was measured with the aid of the Koopman formulas [16].

Questionnaires

Children <12 years old answered, with their parents, the Childhood Asthma Control Test (C-ACT) at the end of the study to measure asthma control. Children ≥12 years old answered the Asthma Control Test (ACT) [17,18].

Children (and parents) were asked for the body posture and head position they

commonly used during inhaling medication at home.
Children were also asked for any possible discomfort during the forward leaning posture.

Sample size calculation
A previous study with a comparable design showed an average fall in FEV_1 of 30% (SD ± 15%) after the exercise challenge test in the placebo group [19]. The intervention group received a high dose inhaled corticosteroid (1000µg fluticasone propionate) with the standard posture before the ECT and showed an average fall in FEV_1 of 20% (SD ± 15%).
Reviewing the literature about the acute effects of a single dose ICS we concluded that a range of high doses all had a comparable effect which implies these doses are on the flat part of the dose response curve. We chose a low dose to be on the steep part of the dose response curve in order to maximise the contrast between inhaling in the different body postures. Also we adjusted the choice of our dose of BDP to the better deposition of BDP compared to fluticasone propionate. We hypothesized that inhalation of 200µg BDP with the standard posture before an exercise challenge test would not protect against EIB and would be comparable to the placebo group of Driessen et al. [19]. We hypothesized inhalation of 200µg BDP with the forward leaning posture would have the same protective effect against EIB compared to a high dose inhaled steroid used in the study of Driessen et al. A sample size of 32 achieves 81% power to detect a difference of 7.5% in fall in FEV_1 between the null hypothesis mean of 30.0% and the alternative hypothesis mean of 22.5% with a known standard deviation of 15.0% and with a significance (alpha) of 0,05 using a two-sided one-sample t-test.
To take possible drop outs into account we aimed to include 38 children.

Statistical analyses
Best values of spirometric measurements were used for statistical calculations. EIB was defined as an exercise induced fall of ≥13% in FEV_1 or $FEV_{0.5}$ compared to baseline value. Results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (minimum; maximum) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal. Within person changes in continuous variables (e.g. fall in FEV_1 or $FEV_{0,5}$) were analysed with a paired T-test or a Wilcoxon signed rank, as appropriate. Between-group comparisons of nominal or ordinal variables were performed by Chi-square tests. For the analysis of correlated proportions a McNemar test was used. To assess the correlation between two continuous variables Pearson's correlation coefficient was computed. A possible period effect was analysed with the Hills and Armitage test. A two-sided value of $P < 0.05$ was considered statistically significant. Data was analysed with SPSS® for Windows® version 21 (IBM, Chicago, IL, USA) analytical software.

Ethical considerations
This study was approved by the Ethics Review Board Twente. All children and parents/guardians received written subject information and provided written informed consent to participate in this study.

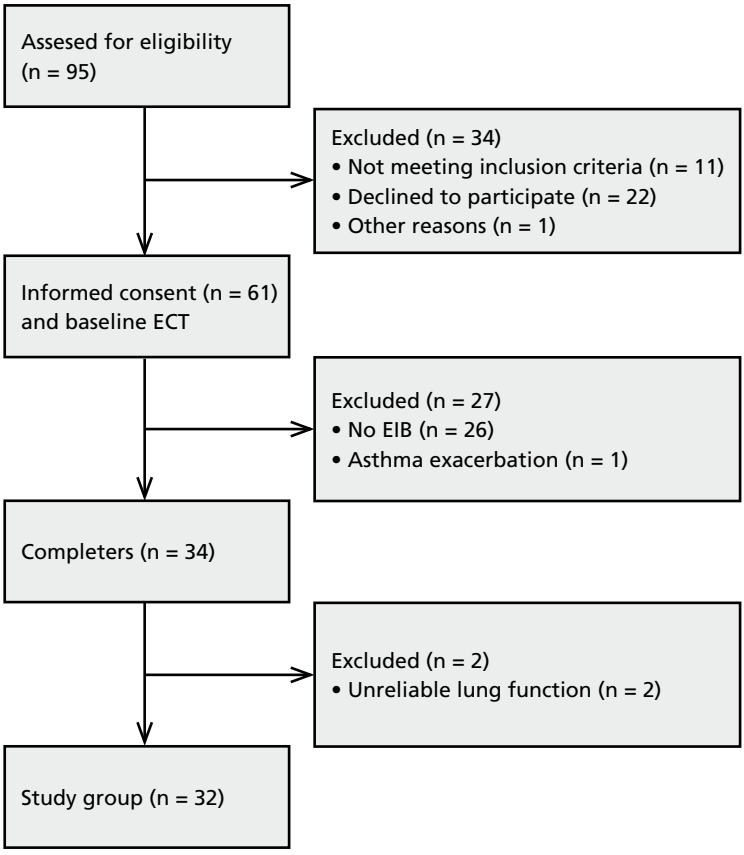


Figure 2. Flow chart of inclusion.

RESULTS

Of the 95 eligible subjects, 22 declined to participate; the majority for logistical reasons.
32 Children (23 boys, mean age 8.8 years, range 5-16) composed the study group (Fig. 2).
No period effects or carry over effects were observed in this study (all p values > 0.33).

25 Children (78.1%) performed the ECT's on the jumping castle. Mean FEV_1 or $FEV_{0.5}$ as a percentage of predicted (FEV_1 or $FEV_{0.5}$%predicted) was 81.3% ± 10.5%. 23 Children (71.9%) had well controlled asthma. Table 1 summarizes all baseline characteristics.
Baseline mean FEV_1 or $FEV_{0.5}$% predicted did not differ significantly between both ECT's (standard posture 78.7% ± 14.7%, forward leaning posture 76.0% ± 13.4% (difference 2.7% (95CI 1.7; 7.1%); p = 0.22). Inhaling ICS in a forward leaning posture provided significantly more bronchodilatation compared to inhaling in the standard posture (respectively 5% ± 9.4% vs. 1.1% ± 7.8%; difference 3.9%

Table 1: Baseline characteristics.

Number of patients	32
Age, years (mean, SD)	8.8 ± 2.9
Boys (N, %)	23 (71.9)
$FEV_{1\ or\ 0.5}$%predicted (mean, SD)	81.3 ± 10.5
$FEV_{1\ or\ 0.5}$ fall (mean, SD)	35.0 ± 14.3
Hospitalisation before the study (N, %)	14 (23.8)
Jumping castle (N, %)	25 (78.1)
Leukotriene receptor antagonist (N, %)	4 (12.5)
Allergy	
- Proven (N, %)	22 (68.8)
- Unknown (N, %)	10 (31.3)
(C)-ACT baseline score (mean, SD)	20.9 ± 4.0
(C)-ACT ≤ 19 (N, %)	9 (28.1)

$FEV_{1\ or\ 0.5}$: forced expiratory volume in 1 or 0.5 s, percentage of predicted based on the reference values of Koopman et al. [16]; Allergy: proven by radioallergosorbent test or skin prick test; (C)-ACT = (Childhood)Asthma Control Test: a score ≤ 19 indicates uncontrolled asthma [17,18].

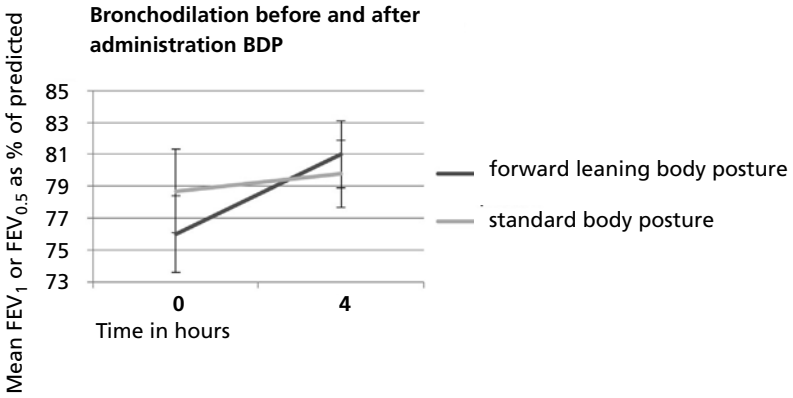


Figure 3. Bronchodilation in both body postures before and after administration of 200µg BDP.
Error bars represent Standard Error. Standard posture: p = 0.420 (95CI -0.039; 0.017). Forward leaning posture: p = 0.005 (95CI -0.084; -0.017). Improvement FEV_1 or $FEV_{0.5}$ as % of predicted was significantly higher in the forward leaning posture: p = 0.041 (95CI -0.076; -0.002).

(95CI 0.2; 7.6%); p = 0.04). Fig. 3 shows the bronchodilatation in both body postures before and after administration of 200µg BDP.
Median fall in FEV_1 or $FEV_{0.5}$ did not differ significantly between the standard posture and forward leaning posture (respectively 16.7% (IQR 9.0%; 24.2%) and 15.1% (IQR 9.9%; 26.9%), difference 1.6%, p = 0.83).
The number of children showing EIB after administration of 200µg BDP in the

Table 2: Nadir and recovery time in the standard and forward leaning body posture

	Standard body posture	Forward leaning body posture	Difference	P-value (95CI)
Nadir	97 s ± 46	148 s ± 58	51 s	P = 0.01 (15.0; 86.6)
Recovery	15.5 min ± 6.8	15.9 min ± 6.1	0.4 min	P = 0.79 (-2.64; 3,41)

Data expressed as mean ± SD. Nadir: time after exercise to maximum fall in FEV_1 or $FEV_{0.5}$ (time in seconds). Recovery: time after exercise of recovery of FEV_1 or $FEV_{0.5}$ within 5% of baseline (time in minutes).

standard posture (18 children, 56.3%) did not differ from the forward leaning posture (19 children, 59.4%).
The protection of 200µg inhaled BDP in the forward leaning posture on EIB was not correlated to the bronchodilating effect of 200µg inhaled BDP as described above (p = 0.33, r = 0.179).
The time to maximum fall in FEV_1 (nadir) in the forward leaning posture was significantly later compared to the standard posture (respectively 2.5 min ± 1.0 min vs. 1.6 min ± 0.8 min; difference 0.9 min (95CI 0.25; 1.44 min); p = 0.01).
Table 2 shows the differences in nadir and recovery time between the two body postures.

3.1. Questionnaires

In the home situation nearly all children inhaled in the sitting or standing upright position with the head horizontal. One child received medication while he was lying, and one child pushed her head in anteflexion. One child could not answer the questionnaire because he did not use medication at home. Twenty three children experienced no bodily discomfort in the forward leaning posture. The other nine experienced a little discomfort, especially in the neck and back.

DISCUSSION

Inhalation of a single dose BDP in both the forward leaning posture and the standard posture had similar efficacy against EIB in asthmatic children.
To our knowledge, this is the first prospective intervention study investigating the protective effect of a low single dose of BDP inhaled in different body postures on EIB in steroid naïve asthmatic children. Recently, BAI's gained popularity as they are child friendly and easy to handle. A drawback however is the massive impaction in the oropharynx. Previously, we and others showed that a high single dose of ICS reduced EIB [7-10].We speculated that inhaling a low dose of ICS in a forward leaning posture, but not in the standard posture, would also provide protection against EIB. However, we found a similar efficacy against EIB in both body postures. The magnitude of the effect was similar compared to previous studies with a high single dose of ICS. The protective effect against EIB of a low dose BDP inhaled in the standard posture is recently published by our study group [20].

The protective effect of a single dose of ICS in asthmatic children on EIB is probably mediated by the acute vasoconstrictive effect of ICS on the hypertrophied and reactive hyperplastic capillary bed of inflamed airways of asthmatics. Kippelen et al. showed that a single dose of beclomethasone also blocked the release of mast cell mediators, such as PGD2, leading to airway narrowing [8].
We observed a small, clinically non relevant, but significantly stronger bronchodilating effect of inhaling 200µg BDP in the forward leaning posture compared to inhaling in the standard posture. Previous studies found a similar acute bronchodilating effect, but with a high single dose of ICS in a standard posture in steroid naïve asthmatic children and adults (1000-1600µg) [21-24].
Children's EIB differs from adult's EIB. The time after exercise to maximal fall of FEV_1 is relatively short [13]. A small minority of children show also breakthrough exercise induced asthma, i.e. a decline in lung function of ≥13% during exercise [13]. This may lead to dropping out of exercise during play and sports. Resuming of exercise before the maximum fall in FEV_1 reopens the airways and may preclude children from dropping out [25]. So, inhaling a single dose of BDP in the forward leaning posture which significantly delayed the fall in FEV_1 from 1.6 min to 2.5 min after exercise is clinically profitable for children. Apparently, the forward leaning posture during inhalation of ICS reinforced bronchodilatory influences during exercise possibly by a higher pulmonary deposition of ICS.
Dubus et al. showed that 60% of asthmatic children using inhaled BDP or budesonide reported local side effects such as coughing, hoarseness, dysphonia and oral candidiasis [2]. A forward leaning posture leading to less impaction of inhaled medication in the upper airway could reduce side effects.
Brandao et al. showed a faster recovery of lung function after inhaling nebulised bronchodilators in a forward leaning posture during an asthma exacerbation in asthmatic adults compared to inhaling in a standard posture [3]. Indeed Listro et al. showed a trend towards less airway resistance when the head was extended in a small study of healthy adults [26]. Nebulising in a forward leaning posture implicates breathing in this posture, whereas our children only inhaled in the forward leaning posture. A sustained period of time breathing may have influenced pulmonary mechanics as well, resulting in a faster recovery of lung function.
The main strengths of our study include the homogenous group of steroid naïve asthmatic children. Additionally, the same investigator performed all ECT's within a period of 2 weeks in a standardised cold air condition reflecting the mean outdoor condition in The Netherlands. This investigator was blinded to the body posture in which the children had inhaled their medication. Limitations of our study are the selection of steroid naïve asthmatic children, and the study design which precludes blinding of the children regarding body posture.
A future study should investigate the effect of inhaling a lower dose of BDP (100µg) in a forward leaning posture on EIB, aiming to be on the steep part of the dose response curve.

CONCLUSIONS

In conclusion, inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in

asthmatic children. The forward leaning posture resulted in postponed EIB compared to the standard posture which is clinically profitable for children during play and sports. This suggests that body posture during inhalation can influence effects of inhaled medication, probably by a change in pulmonary deposition.

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Chapter 7

Protective effect of a low single dose inhaled steroid against exercise induced bronchoconstriction

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SUMMARY

Objective
Daily use of inhaled corticosteroids (ICS) reduces exercise induced bronchoconstriction (EIB) in asthmatic children. A high single dose of ICS also provides acute protection against EIB. Objective of this study was to investigate whether a low single dose of ICS offers protection against EIB in asthmatic children.

Methods
31 Mild asthmatic children not currently treated with inhaled corticosteroids, 5–16 years, with EIB (fall in FEV_1 or $FEV_{0.5}$ ≥13%) were included in a prospective intervention study. They performed two ECT's within 2 weeks. Four hours before the second test children inhaled 200µg beclomethasone-dipropionate (BDP) with a breath-actuated inhaler (BAI).

Results
The median fall in FEV_1 or $FEV_{0.5}$ after 200µg BDP was significantly reduced from 30.9% at baseline to 16.0% ($P<0.001$). Twenty children (64.5%) showed a good response to 200µg BDP (≥50% decrease in fall of FEV_1 or $FEV_{0.5}$), while 8 children showed a moderate response (25–50%), and three children showed no response at all (< 25%).

Conclusion
A low single dose of ICS offers acute protection against EIB in the majority of asthmatic children not currently treated with inhaled corticosteroids.

INTRODUCTION

Exercise induced bronchoconstriction (EIB) is defined as a transient narrowing of the airway during or after physical exercise [1]. EIB is a highly prevalent and specific symptom of childhood asthma and reflects airway inflammation [1,2].
Of all asthma symptoms, EIB is considered to be the most detrimental on the quality of life of children [3,4].
An exercise challenge test (ECT) can detect EIB, diagnose asthma and evaluate asthma treatment [5]. Daily use of inhaled corticosteroids (ICS) reduces exercise induced bronchoconstriction (EIB) in asthmatic children. Thio et al. also showed an acute protective effect of a high single dose of ICS in asthmatic children not currently treated with inhaled corticosteroids [6]. The effect, however, of a low single dose of ICS against EIB is unknown.
The aim of this study was to investigate the protective effect against EIB of 200µg beclomethasone-dipropionate (BDP) inhaled 4 hr prior to an ECT in asthmatic children not currently treated with inhaled corticosteroids. The secondary aim was to identify individual characteristics of children responding to a single dose ICS.

METHODS

Patients

Children 5–16 years, with a pediatrician's diagnosis of mild asthma based on GINA guidelines were recruited from the outpatient clinic of the pediatric department of Medisch Spectrum Twente, Enschede, the Netherlands, from October 2013 to February 2014 [7]. All children had asthmatic symptoms for more than one year. None of the children had used ICS or nasal corticosteroids for at least two months prior to the study. Half of the children had never used ICS before, the other half had stopped ICS based on symptoms. All children performed an ECT to assess for EIB and when EIB was identified, confirming the diagnosis of asthma, children proceeded to the second ECT. Children with other pulmonary or cardiac disorders were excluded. Children being admitted to the hospital or being prescribed systemic corticosteroids because of an exacerbation in the last 2 months prior to the ECT were excluded.

First exercise challenge test

The ECT's were performed as previously described by Van Leeuwen et al. and Driessen et al [8,9]. In summary children 5–10 years old jumped for a maximum of 6 min on a jumping castle in cold, dry air conditions (9.5–10 degrees and humidity 57–59%) in an indoor ice skating rink. Children 12–16 years old performed the ECT on a treadmill with a 10° slope (Trimline® 7150). Children 10–12 years old could choose between the two ECT formats. Heart rate was continuously monitored by a radiographic device (Garmin Forerunner 610) and target was to achieve 80–90% of maximum heart rate. Pulmonary function was measured before, during and after exercise using standard ERS protocol [10] in case of an ECT on the jumping castle and in case of running on the treadmill only before and after the ECT. An exercise induced fall in FEV_1 of ≥13% (or $FEV_{0.5}$ if FEV_1 was not reproducible in the

youngest children) compared to baseline was considered as positive for EIB [11]. The percentage of predicted baseline FEV_1 or $FEV_{0.5}$ was measured with the aid of the Koopman formulas [12].

Second exercise challenge test

Children performed the second ECT according to the aforementioned procedure within two weeks after the baseline ECT. This ECT was preceded by the inhalation of 200µg BDP (Qvar®) 4 hr prior to the ECT, administered with a breath-actuated inhaler (BAI). In the hours between the medication administration and the ECT the child was not allowed to perform exercise, so parents had to take their child to the ice skating rink by car and older children could arrive by bus or scooter.
The degree of protection of BDP against EIB was assessed for each individual child. Mean protection was defined as ((fall in FEV_1 or $FEV_{0.5}$ at baseline-fall in FEV_1 or $FEV_{0.5}$ after BDP)/ fall in FEV_1 or $FEV_{0.5}$ at baseline) [13]. Children with a decrease in fall of FEV_1 or $FEV_{0.5}$ of 50% were classified as responders, a decrease of 25–50% was classified as a moderate response and non-responders were children with a decrease of <25% in fall of FEV_1 or $FEV_{0.5}$.

Questionnaire

Children <12 years old, together with their parents, answered the Childhood Asthma Control Test (C-ACT) at the end of the study to measure asthma control [14]. Children ≥12 years old answered the Asthma Control Test (ACT) [15].

Sample size calculation

This study was part of another study on EIB, which included 32 patients. Given a sample size of 31 patients, a power of 90%, an alpha of 5% and an expected standard deviation in the fall in FEV_1 or $FEV_{0.5}$ of 15%, [16] the smallest detectable difference in fall in FEV_1 or $FEV_{0.5}$ between the baseline ECT and the ECT after inhaling BDP was 9.03%.

Statistical analyses

Best values of spirometric measurements were used for statistical calculations. EIB was defined as an exercise induced fall of ≥13% in FEV_1 or $FEV_{0.5}$ compared to baseline value. Results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (minimum; maximum) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal. Within person changes in continuous variables (e.g. fall in FEV_1 or $FEV_{0.5}$) were analysed with a paired T-test or a Wilcoxon signed rank, as appropriate. Between-group differences (responders versus non-responders) in continuous variables (e.g. age) were analysed with a independent T-test or a Mann-Whitney U test, as appropriate. Between-group comparisons of nominal or ordinal variables (e.g. gender) were performed by Chi-square tests. A two-sided value of $P<0.05$ was considered statistically significant. Data were analyzed with SPSS® for Windows® version 20 (IBM, Chicago, IL) analytical software.

Ethical considerations

This study was approved by the Medical Ethics Review Board Twente. All children

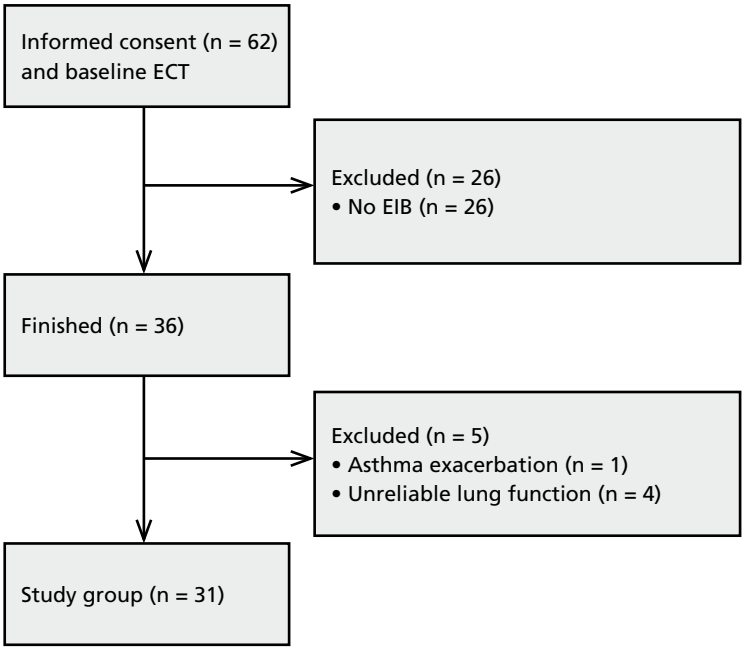

Figure 1. Flow chart of inclusion.

Table 1: Baseline characteristics of the study group

Number of patients	31
Age, years (mean ± SD)	8.6 ± 2.8
Boys (N (%))	22 (71)
Hospitalization before the study (N (%))	13 (41.9)
FEV_1 or $FEV_{0.5}$ % predicted (mean ± SD)	81.9 ± 10.2
FEV_1 or $FEV_{0.5}$ fall in % (median, IQR)	30.9 (21.8; 49.5)
Breakthrough asthma (N (%))	15 (48.4)
Exercise test format	
- Jumping castle (N (%))	25 (80.6)
- Treadmill (N (%))	6 (19.4)
Short acting bronchodilator agent p.r.n. (N (%))	31 (100)
Leukotriene receptor antagonist (N %))	3 (9.7)
Allergy	
- Proven (N (%))	21 (67.7)
- Unknown (N (%))	10 (32.3)
(C-)ACT ≤ 19 (N (%))	8 (25.8)
(C-)ACT baseline score (mean ± SD)	21.1 ± 3.9

Data are expressed as mean values ± standard deviation, median + interquartile range (IQR) or numbers (percentage); FEV_1 or $FEV_{0.5}$: forced expiratory volume in 0.5 or 1 s, percentage of predicted based on the reference values of Koopman et al.[12] ; Breakthrough asthma: fall in FEV_1 or $FEV_{0.5}$ ≥ 13% during exercise; p.r.n. pro re nata; Allergy: proven by radioallergosorbent test or skin prick test; (C)-ACT=(Childhood)-Asthma Control Test: a score ≤ 19 indicates uncontrolled asthma [14,1].

and parents/guardians received written patient information and provided written informed consent to participate in this study.

RESULTS

Of the 96 eligible patients, 62 patients entered the study after informed consent was obtained. Twenty-six did not show EIB. After finishing the study five children were excluded (four children performed unreliable lung function measurements and one child had a worsening of their asthma) and so 31 (22 boys, mean age 8.6 years, range 5–16), composed the study group (Fig.1). Twenty-five children (80.6%) performed the ECT's on the jumping castle. Mean FEV_1 or $FEV_{0.5}$ as a percentage of predicted was 81.9% ± 10.2%. 23 Children (74.2%) children had well controlled asthma according to the (C)-ACT.

Baseline ECT

All children achieved their target heart rate during the ECT. Mean fall of FEV_1 or $FEV_{0.5}$ was 35.0% ± 14.5%. 35% of the children were too young to perform reliable FEV_1 measurements, so in that case the $FEV_{0.5}$ was reported.

Effects on EIB

After inhalation of 200µg BDP 14 children (45.2%) showed no EIB anymore. Five children (16.1%) still suffered from breakthrough EIB compared to 15 (48.4%) at baseline (P = 0.006).

Children showed a significantly smaller fall of FEV_1 or $FEV_{0.5}$ after inhaling 200µg BDP (median fall 16.0% IQR 8.6 ; 24.2%) compared to the baseline ECT (median fall 30.9% IQR 21.8 ; 49.5%, P = <0.001). Mean protection of BDP against EIB was 48.9% ± 32.6%. Twenty children (64.5%) showed a good response (≥50% decrease in fall of FEV_1 or $FEV_{0.5}$) to a low single dose BDP. Eight children (25.8%) showed a moderate response (25–50% decrease in fall of FEV_1 or $FEV_{0.5}$), while three children

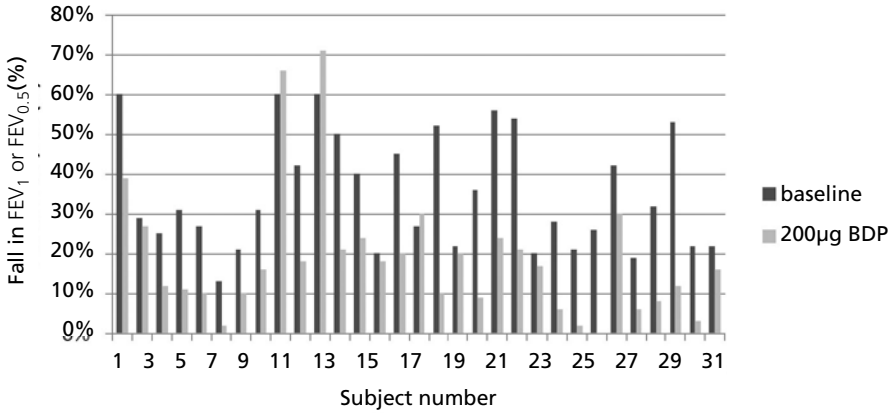

Figure 2. Individual responses to a low single dose BDP measured in fall in FEV_1 or $FEV_{0.5}$.

Table 2: Characteristics of Responders versus Moderate/non-responders to a Single Low Dose Beclomethasone Dipropionate on Exercise Induced Bronchoconstriction

	Responders	Moderate/non-responders	Diff (95%CI); p-value
Number of patients	20	11	
Age, years (mean ± SD)[1]	8.3 ± 3.2	9.2 ± 2.0	0.9 (-1.21; 3.16); P=0.370
Boys (N (%))[2]	12 (60.0)	10 (90.9)	P=0.077
Hospitalisation before the study (N (%))[2]	6 (30.0)	7 (63.6)	P=0.076
FEV_1 or $FEV_{0.5}$ % predicted (mean ± SD)[1]	82.4 ± 12.0	81.0 ± 5.9	1.4 (-0.08; 0.05); P=0.669
FEV_1 or $FEV_{0.5}$ fall % (mean ± SD)[1]	34.2 ± 13.5	36.4 ± 16.8	2.2 (-0.09; 0.14); P=0.683
Break through asthma (N (%))[2]	10 (50.0)	5 (45.5)	P=0.553
Exercise test format[2]			
Jumping castle (N (%))	15 (75.0)	10 (90.9)	P=0.284
Treadmill (N (%))	5 (25.0)	1 (9.1)	
Leukotriene receptor antagonist (N (%))[2]	1 (5.0)	2 (18.2)	P=0.281
Allergy[2]			P=0.510
Proven (N (%))	14 (70.0)	7 (63.6)	
Unknown (N (%))	6 (30.0)	4 (36.4)	
(C-) ACT 19 (N (%))[2]	4 (20.0)	4 (36.4)	P=0.281
(C-) ACT baseline score (median (IQR))[3]	22.5 (20.0–24.0)	22.0 (17.0–23.0)	0.5 P=0.670

Responders: decrease in fall in FEV_1 or $FEV_{0.5}$ ≥50% compared to baseline. Moderate responders: decrease in fall in FEV_1 or $FEV_{0.5}$ 25–50% compared to baseline. Non-responders: decrease in fall in FEV_1 or $FEV_{0.5}$ <25% compared to baseline.
FEV_1 or $FEV_{0.5}$: forced expiratory volume in 0.5 or 1 s, percentage of predicted based on the reference values of Koopman et al.[12] ; Breakthrough asthma: fall in FEV_1 or $FEV_{0.5}$ ≥13% during exercise. Allergy: proven by blood test or skin prick test; (C)-ACT, (Childhood)-Asthma Control Test: a score ≤19 indicates uncontrolled asthma.[14,15]

[1] Independent T-test.

[2] Chi-square test.

[3] Mann-Whitney U test.

(9.7%) showed no response at all (<25% decrease in fall of FEV_1 or $FEV_{0.5}$). Individual responses to BDP are summarized in Figure 2.
Baseline characteristics of the responder and moderate/ non-responder group are shown in Table 2. None of these baseline characteristics differed significantly between the two groups, but the non-responder group showed a trend towards more boys (P = 0.077) and a higher amount of children being hospitalized because of asthma before the study (P = 0.076).
Test results of the baseline ECT and the ECT after inhaling 200µg BDP are summarized in Table 3.

Nadir and recovery of EIB

Of the 17 children still showing EIB after inhaling 200µg BDP, the maximum fall of FEV_1 or $FEV_{0.5}$ (nadir) appeared significantly earlier after inhaling BDP (108 sec ± 66) compared to baseline (162 sec ± 90) (difference 54 sec, 95%CI 5.5 ; 93.4, P = 0.03). Also, the recovery time of these 17 children (FEV_1 or $FEV_{0.5}$ within 5% of baseline) was significantly shorter after inhaling 200µg BDP compared to baseline (19.7 min ± 4.5 and 14.9min ± 6.9, respectively; difference 4.8 min, 95%CI 1.4; 8.1, P = 0.009).

DISCUSSION

A low single dose of 200µg BDP inhaled 4 hr prior to an ECT protected significantly against EIB in asthmatic children not currently treated with inhaled corticosteroids. There was however a considerable variability in the protection against EIB, with a trend towards more boys in the non-responder group.
To our knowledge, this is the first prospective intervention study investigating the acute protective effect of a low single dose of 200µg BDP 4 hr prior to an ECT on EIB in asthmatic children. Our results correspond to Thio et al. who showed that a

Table 3: Test results at baseline and after inhalation of 200µg of beclomethasone dipropionate (BDP)

	Baseline	After 200 mg BDP	Diff (95%CI); P-value
FEV_1 or $FEV_{0.5}$ % of predicted value (mean ± SD)[1]	81.9 ± 1.2	80.0 ± 12.8	1.9 (-0.02; 0.054); P=0.278
FEV_1 or $FEV_{0.5}$ fall % (median (IQR))[2]	30.9 (21.8; 49.5)	16.0 (8.6; 24.2)	P≤0.001
Break through asthma (N (%))[3]	15 (48.4)	5 (16.1)	P=0.006
Nadir in seconds (mean ± SD)[1]	162 ± 90	108 ± 66	54 (5.5; 93.4); P=0.030
Recovery in minutes (mean ± SD)[1]	19.7 ± 4.5	14.9 ± 6.9	4.8 (1.4; 8.1); P=0.009

Data expressed as mean values ± standard deviation, median with interquartile ranges or numbers (percentage). BDP: Beclomethasone Dipropionate. FEV_1 or $FEV_{0.5}$: forced expiratory volume in 0.5 or 1 s, percentage of predicted based on the reference values of Koopman et al.[12]; Breakthrough asthma: fall in FEV_1 or $FEV_{0.5}$ ≥13% during exercise.
[1] Independent T-test.
[2] Mann-Whitney U test.
[3] Chi-square test.

single high dose of 1 mg fluticasone 4 hr before an ECT offered an acute protective effect against EIB in asthmatic children.[6] Other studies also showed an acute protection against bronchial hyperresponsiveness (BHR) to indirect stimuli when using high single doses of 1000–1600µg ICS inhaled 4–8 hr before a challenge in adult asthmatics [17,18]. Kippelen et al. demonstrated that a high single dose of 1500µg BDP provided significant protection against BHR due to hyperpnea in both untrained adult asthmatics and athletes with EIB.[18]

We showed that a low single dose of 200µg BDP provided ≥50% protection in the majority of children indicating that the effect of 200µg BDP is already on the flat part of the dose-response curve.

The protective effect of a low single dose ICS against EIB may be clinically profitable for mild asthmatic children who do not require maintenance ICS therapy but with EIB. Bronchoprotection of salbutamol against EIB is, although stronger, short lived and subject to tachyphylaxis [19–21].

There is no agreement regarding the nature of the exact stimulus that causes EIB. 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 mucosal mast cells, resulting in bronchial obstruction [1,22]. The second hypothesis states that exercise-induced hyperventilation results in airway cooling and vasoconstriction. After exercise, when ventilation has normalized, the airways rapidly re-warm leading to vascular engorgement and mucosal edema resulting in bronchial obstruction [1,23]. Since topical steroids have a potent vasoconstrictive effect, the protective effect of a single inhaled dose of BDP against EIB suggests that bronchovascular engorgement and mucosal oedema do play a substantial role in the pathophysiology of EIB. The variability of the response to BDP observed in our study suggests that the relative contribution of vascular engorgement and mucosal edema to airway obstruction may vary from person to person underlining the heterogeneity of asthma in childhood. We were surprised to find a trend towards more boys in the non-responder group which may be due to smaller airways of prepuberal boys compared to girls [24].

The main strengths of our study include the homogenous group of 31 asthmatic children not currently treated with inhaled corticosteroids. All ECT's were performed in the same setting by the same investigator. Also, a short time period between the two interventions was pursued (<2 weeks) and all tests were carried out by the same investigator in standardized air conditions. Medication administration was supervised by the same investigator in all children.

Limitations of our study were the absence of a placebo group and the fact that the investigator was not blinded to the use of BDP prior to the ECT. The FEV_1 or $FEV_{0.5}$ as a % of predicted value, prior to the ECT, did not differ between the two ECT's. The reason for this design was explained by the fact that this analysis was part of a more extensive study that analysed the influence of body posture during inhaling BDP prior to an ECT on EIB. In eight children we found severe EIB (fall in FEV_1 or $FEV_{0.5}$ ≥50%) which was not compatible with mild asthma and did reflect marked airway inflammation. These children were started on maintenance ICS after the study. Severity of EIB as measured with fall in FEV_1 does not correlate well with symptoms as measured with the ACT questionnaire [25].

The acute response of a single dose ICS in asthmatic children we observed may have

implications for guidelines relating to medication restrictions before broncho-provocative tests. Further dose response studies including different time points after single dosing ICS in asthmatic children with or without maintenance ICS could provide data about the sustained effect of a single dose ICS. Further studies could also investigate if asthmatic children with EIB, without other symptoms of asthma, could profit from the acute effect of a low single dose ICS in the morning.
In conclusion, a low single dose of 200µg BDP inhaled 4 hr prior to an ECT offered acute protection against EIB in the majority of asthmatic children not currently treated with inhaled corticosteroids.

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Chapter 8

Salbutamol and exercise induced inspiratory flow limitation in asthmatic children

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ABSTRACT

Objective
Exercise induced bronchoconstriction (EIB) is a frequent and specific symptom of childhood asthma featured by expiratory flow limitation. A recent study showed that exercise can also induce inspiratory flow limitation, independent of EIB. The aim of this study was to investigate whether salbutamol protects against exercise induced inspiratory flow limitation in asthmatic children.

Methods
The study had a prospective double-blind placebo-controlled randomized cross-over design. Children 8-16 years old with documented exercise induced inspiratory flow limitation performed two exercise challenge tests (ECT's) preceded by the inhalation of 200µg salbutamol or placebo. EIB was defined as a fall in forced expiratory volume in 1 second (FEV_1) ≥ 13% whereas inspiratory flow limitation was defined as a fall in mid inspiratory flow (MIF_{50}) ≥ 25%.

Results
63% of the children (19/30) with exercise induced flow limitation showed an inspiratory flow limitation. Salbutamol significantly reduced the mean exercise induced fall in MIF_{50} in children with exercise induced inspiratory flow limitation compared to placebo (17.6% versus 24.9%, p=0.004).

Conclusions
We observed a significant but inconsistent, individually variable protection of salbutamol against exercise induced inspiratory flow limitation in contrast to the consistent protective effect of salbutamol against EIB. We confirmed that a substantial number of the children with exercise induced flow limitation have an inspiratory flow limitation. Asthmatic children who experience persistent exercise induced asthmatic symptoms despite the use of (prophylactic) salbutamol, may suffer from an inspiratory flow limitation as a component of their asthma.

INTRODUCTION

Exercise induced bronchoconstriction (EIB) is a specific and common symptom of childhood asthma and of all asthma symptoms, considered to be the most detrimental on quality of life [1-3]. EIB is a sign of bronchial hyperresponsiveness (BHR) and featured by bronchial obstruction leading to expiratory flow limitation. Recent studies have shown that an exercise challenge test not only can induce EIB but also can induce inspiratory flow limitation[4-8]. Exercise induced inspiratory flow limitation is independent from EIB and also occurs after exercise. It is a different clinical entity than vocal cord dysfunction (VCD) which is accompanied by acute choking or an inspiratory stridor during exercise [4,5,7,8]. Inspiratory flow limitation is defined as a fall in mid inspiratory flow (MIF_{50}) of more than 25%[4,7,8]. Several studies have shown that inspiratory flow limitation can be induced by airway challenge tests other than exercise.

Exercise induces the release of mediators from inflammatory cells resident in the airway mucosa. These mediators are responsible for bronchial narrowing by activation of the inflammatory response in the asthmatic airway. Inhaled salbutamol stabilizes inflammatory cells and can therefore provide excellent protection [1,9]. The pathofysiology of exercise induced inspiratory flow limitation is unknown but inflammatory mediators released may be directly or indirectly involved. We hypothesized that salbutamol protects against inspiratory flow limitation implicating that inflammatory mediators are involved in the pathofysiology of inspiratory flow limitation.

The aim of this study was to investigate whether 200µg salbutamol protects against exercise induced inspiratory flow limitation in asthmatic children. The secondary aim was to investigate the relation between the protective effect of salbutamol against EIB and against exercise induced inspiratory flow limitation.

MATERIALS & METHODS

Patients

The study had a prospective double-blind placebo-controlled randomized cross-over design. Children 8 - 16 years with asthma, diagnosed by a pediatrician, were recruited from the outpatient clinic of the pediatric department of Medisch Spectrum Twente, Enschede (MST) from October 2013 to February 2014. Children were eligible if they demonstrated exercise induced inspiratory flow limitation with or without EIB during an exercise challenge test (ECT) within a period of two weeks prior to the study [10]. There were no restrictions to the use of medication, but children had to cease long acting bronchodilators or leukotriene antagonists 24 hours and short acting bronchodilators 8 hours before the ECT [5,11]. Children were excluded if they were admitted to the hospital or being prescribed systemic corticosteroids because of an exacerbation in the last eight weeks prior to the screening ECT.

Randomization and blinding

For randomization block sizes of 2 and 4 children were used. The randomization list was designed with the aid of a computerized randomization method (Windows version 6.0 randomization program "Rand.exe" by Steven Piantadosi) performed

by an independent assistant. To ensure concealment of allocation, the randomization scheme was managed by an independent assistant (secretary of pediatric department) and was not accessible to the researchers.
The administration of either salbutamol or a placebo prior to the exercise challenge test was inserted in a double-blind design and also the statistical analysis was performed blinded. TEVA pharmaceuticals provided the salbutamol and the placebo Autohalers®. Labeling to arrange the double-blinded design was performed under the conditions of good manufacturing practice by an external hospital. The inhalers were marked with codes which were kept in a sealed envelope by a secretary.

Exercise challenge test

To minimize anxiety which can lead to failed tests, the youngest children exercised on a jumping castle and the older children who were comfortable on a treadmill. For both exercise formats the same exercise challenge test guidelines were used[1,11]. During the four hours prior to the ECT's, children were not allowed to perform strenuous exercise.
After the screening ECT in which inspiratory flow limitation was assessed, the included children were randomized to perform two ECT's. The both ECTS's were preceded by the inhalation of 200µg salbutamol (Airomir® Autohaler) or placebo in a randomized order fifteen minutes prior to the ECT.
ECT's were planned after each other with a minimum interval time of 2 days and a maximum of 14 days. ECT's and pulmonary function measurements were performed as previously described[5,11]. Children performed baseline spirometry measurements using a Microloop MK8 Spirometer (ML3535) according to the standard ERS protocol [12]. Koopman reference values were used to calculate the predicted value of FEV_1 [13]. After baseline spirometry children inhaled either 200µg salbutamol (Airomir® Autohaler) or placebo under supervision of the investigator to ensure correct technique. Fifteen minutes after inhaling children performed spirometry measurements again. Thereafter, children aged 8-10 years old jumped for a maximum of 6 minutes on a jumping castle in cold, dry air conditions (9.5-10 degrees Celsius and a relative humidity of 57-59%) in an indoor ice skating rink. Children aged 12-16 years old performed the ECT on a treadmill with a 10° slope (Trimline® 7150) under the same air conditions. Children aged 10-12 years old could choose between the two ECT formats. Heart rate was continuously monitored by a radiographic device (Garmin Forerunner 610) and the target was to achieve 80-90% of their maximum heart rate. An exercise induced fall in FEV_1 of ≥13% compared to baseline was considered as positive for EIB[10]. For a reliable measurement of the MIF_{50} the forced inspiratory vital capacity had to be within 7.5% of the forced expiratory vital capacity. A fall in MIF_{50} of ≥25% compared to baseline in more than one consecutive measurement was considered positive for an inspiratory flow limitation[5,7].
The degree of protection of salbutamol against exercise induced inspiratory flow limitation was assessed for each individual child based on the MIF_{50}. Children with a protection of fall in MIF_{50} of ≥50% were classified as responders to therapy i.e. if the MIF_{50} during the salbutamol ECT did not fall at least 50% compared to the placebo ECT, the child was considered as a responder. Children with a protection of fall in MIF_{50} of <50% were classified as non-responders to therapy.

Questionnaire

Children < 12 years old and their parents filled out the Childhood Asthma Control Test (C-ACT) to measure asthma control. Children > 12 years old filled out the Asthma Control Test (ACT) [14,15].

Sample size calculation

A previous study investigating exercise induced inspiratory flow limitation in our clinic showed that 46% of asthmatic children (mean age 13.2 years old with a SD 2,2 years) had an exercised induced inspiratory flow limitation. The average fall in MIF_{50} was 25.8% (SD ±16.1%) after the exercise challenge test[5].

We hypothesize that inhalation of 200µg salbutamol prior to the ECT would offer a clinical relevant protection of 50% against inspiratory flow limitation. To document this significant difference in fall of MIF_{50} with a paired T-test we did a power calculation.

Assuming an average fall in MIF_{50} of 25% (SD ±16%) in the placebo condition and an average fall in MIF_{50} of 12.5% (SD ±16%) when 200µg salbutamol is administered prior to the ECT, and assuming a significance level (alpha) of 0.05 and a power of 80%, 15 patients would be needed in a cross-over design.

Statistical analyses

Best values of spirometric measurements were used for statistical calculations. Results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (minimum; maximum) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal.

Within person changes in continuous variables (e.g. fall in FEV_1 or MIF_{50}) were analyzed with a paired T-test or a Wilcoxon signed rank, as appropriate. Between group differences in continuous variables were analyzed with an unpaired T-test (e.g. responders versus non-responders). Between-group comparisons of nominal or ordinal variables were performed by Chi-square tests (e.g. responders versus non-responders). To assess the correlation between two continuous variables (e.g. protection of salbutamol against EIB and inspiratory flow limitation) Spearman's rho was computed. A possible period or carry over effect was analyzed with the Hills and Armitage test. A 2 sided value of $P < 0.05$ was considered statistically significant. Data was analyzed with SPSS® for Windows® version 20 (IBM, Chicago, IL, USA) analytical software.

Ethical Considerations

This study was approved by the hospital ethics review board and the Central Committee on Research Involving Human Subjects (CCMO) and registered in the Dutch Trial Register (http://www.trialregister.nl) number NTR4021. All children and parents/guardians received written patient information and provided written informed consent to participate in this study.

RESULTS

We selected/screened 30 children who showed exercise induced inspiratory flow limitation and/or EIB at the screening ECT within 2 weeks prior to the study. We

Table 1: baseline characteristics

Number of children	16
Age in years (mean ± SD)	11.8 ± 2.2
Male gender (N, (%))	11 (68.8)
Hospitalisation before study (N, (%))	6 (37.5)
ECT format (N, (%))	
- Jumping castle	11 (68.8)
- Treadmill	5 (31.2)
FEV_1 as % of predicted (mean ± SD)[a]	84.9 ± 9.8
Fall in FEV_1 in % (mean ± SD)	27.4 ± 17.1
Fall in MIF_{50} in % (mean ± SD)	39.1 ± 9.6
ICS (N, (%))	15 (93.8)
LTRAs (N, (%))	6 (37.5)
Allergy (N, (%))[b]	
- Positive	9 (56.3)
- Negative	4 (25)
- Unknown	3 (18.8)
(C-)ACT ≤ 19 (N, (%))[c]	8 (50)
Score (C)ACT (mean ± SD)	19.1 ± 4.9

SD: standard deviation; ECT: exercise challenge test; [a]FEV_1: forced expiratory volume in 1sec, percentage of predicted based on the reference values of Koopman et al[13]. MIF_{50}: maximal inspiratory flow at 50 percent of vital capacity. ICS: inhaled corticosteroids. LTRAs: leukotriene receptor antagonists. [b]Allergy: proven by blood test or skin prick test. [c](C-)ACT: (Childhood) Asthma Control Test: a score ≤19 points indicates uncontrolled asthma[14,15].

excluded 11 children (36.7%) with only EIB, but without exercise induced inspiratory flow limitation (fall in MIF_{50} of ≥25%). We included 19 children (63.3%) with exercise induced inspiratory flow limitation with or without EIB. After inclusion 3 children were excluded from the study. One child was excluded because of unreliable lung function measurements, one due to an asthma exacerbation and one

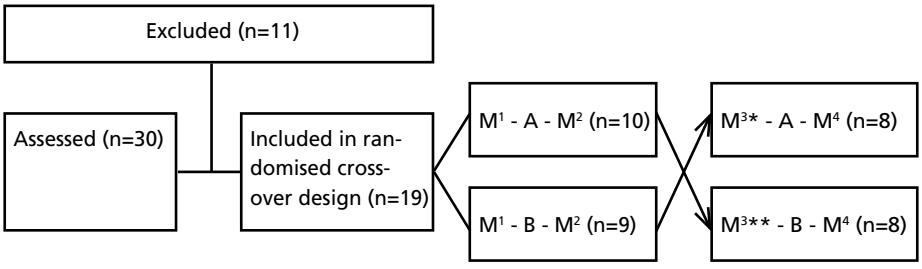

Figure 1: Flow chart of inclusion
M. spirometry measurement with superscript numbers identifying the first, second, third and fourth spirometry
A: 200µg salbutamol
B: 200µg placebo

Table 2: Fall in MIF_{50} and FEV_1 at baseline, with placebo and with salbutamol

					Difference (95% CI); p-value		
		Baseline	Placebo	Salbutamol	Baseline-placebo	Baseline-salbutamol	Placebo-salbutamol
Total study group (n=16)	MIF_{50} (mean ± SD))	39.1 ± 9.6	29.4 ± 10.1	17.6 ± 11.6	9.7 (5.5-14.0) p <0.001	21.5 (15.7-27.3) p <0.001	11.8 (4.3-18.2) p=0.004
	FEV_1 (mean ± SD)	27.4 ± 17.1	22.5 ± 14.8	10.3 ± 7.9	4.9 (1.6-8.0) p=0.006	17.1 (8.1-25.9) p=0.001	12.2 (4.1-20.4) p=0.006
Isolated inspiratory flow limitation (n=5)	MIF_{50} (median (IQR))	32.5 (27.3-35.3)	22.5 (17.7-32.1)	10.5 (5.5-18.4)	10.0 p=0.080	22.0 p=0.043	12.0 p=0.080
Combined flow limitation (n=11)	MIF_{50} (median (IQR))	40.3 (32.4-49.8)	29.8 (20.8-41.3)	14.3 (11.6-30.2)	10.5 p=0.008	26.0 p=0.004	15.5 p=0.050
	FEV_1 (mean ± SD)	35.5 ± 14.4	29.5 ± 12.1	13.0 ± 7.9	6.0 (1.70-10.2) p=0.011	22.5 (10.7-34.2) p=0.002	16.5 (4.50-28.0) p=0.012

Data expressed as mean values ± standard deviation, median (interquartile range (IQR)) or p value (95%CI). FEV_1: forced expiratory volume in 1 s. MIF_{50}: mid inspiratory flow at 50 percent of vital capacity.

due to non-adherence with maintenance medication. Sixteen children composed the study group. Figure 1 shows the flow chart of inclusion. Baseline characteristics of the 16 included children are shown in table 1. Hospitalization status indicates hospitalization due to an asthma exacerbation more than eight weeks before the start of the study.

All 16 children performed two ECT's and achieved their target heart rate during their ECT's. Eleven children showed combined EIB with an inspiratory flow limitation, the other 5 children showed an isolated inspiratory flow limitation. The mean time to maximum fall in MIF_{50} was 4.5 min (± 3.9), while the mean time to maximum fall in FEV_1 was 3.6 min (± 2.7). There was a significant correlation between the fall in FEV_1 and the fall in MIF_{50} ($r=0.84$, $p < 0.001$).

No period effects or carry over effects were observed in this study (all p values > 0.43). Salbutamol significantly reduced the mean exercise induced fall in MIF_{50} compared to placebo (17.6% versus 24.9%, p=0.004).

The FEV_1 value as percentage of predicted measured before administration of salbutamol did not significantly differ compared to placebo (4.1%; 95CI:0.0%-8.4%; p = 0.06) or compared to the screening visit (2.9%; 95CI: -1.9%-7.7%; p = 0.22).

Table 3: Characteristics of responders and non-responders

Patient characteristics	Responders	Non-responders
Number of children	8	8
Age, years (mean ± SD)	11.5 ± 2.0	12.0 ± 2.5
Boys (N, %)	6 (75)	5 (62.5)
FEV_1 as % of predicted[a] (mean ± SD)	86.5 ± 12.5	83.3 ± 6.5
Fall in FEV_1 in % at baseline (mean ± SD)	25.9 ± 16.6	28.9 ± 18.6
Fall in MIF_{50} in % at baseline (mean ± SD)	37.0 ± 9.9	41.1 ± 9.3
Hospitalisation before study (N, %)	3 (37.5)	3 (37.5)
ICS (N, %)	7 (87.5)	8 (100)
LTRAs (N, %)	0	6 (75)
Allergy (N, %)[b]		
- proven	5 (62.5)	4 (50.0)
- unknown	1 (12.5)	2 (25.0)
(C)ACT ≤ 19 (N, %)[c]	3 (37.5)	5 (62,5)
Score (C)ACT (mean ± SD)	19.6 ± 5.1	18.6 ± 5.0

Data expressed as mean ± SD, median (IQR) or numbers (percentage). [a] FEV_1 : forced expiratory volume in 1sec, percentage of predicted based on the reference values of Koopman et al [13]. MIF_{50}: maximal inspiratory flow at 50 percent of vital capacity. ICS: inhaled corticosteroids. LTRAs: leukotriene receptor antagonists. [b] Allergy: proven by radioallergosorbent test or blood test. [c] (C)ACT: (Childhood) Asthma Control Test: a score ≤19 points indicates uncontrolled asthma[14,15].

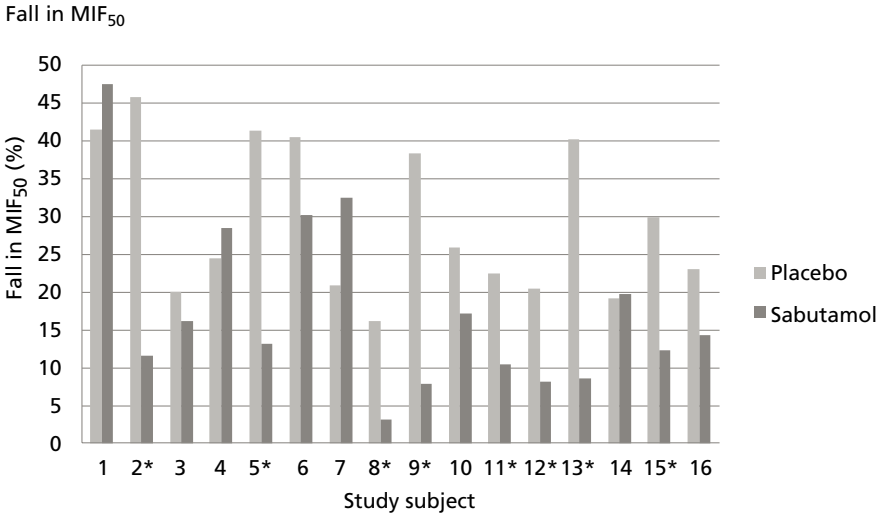

Figure 2. Fall in MIF_{50} in percentage with placebo and with salbutamol for each individual child. MIF_{50}: maximal inspiratory flow at 50 percent of vital capacity. * Children with ≥50% protection on the MIF_{50} with salbutamol.

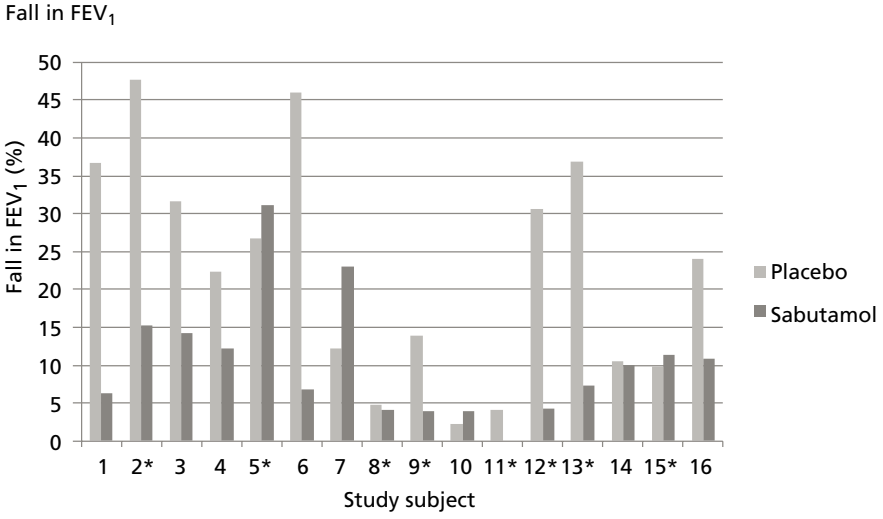

Figure 3. Fall in FEV_1 in percentage with placebo and with salbutamol for each individual child. FEV_1: forced expiratory volume in 1 s. * Children with ≥50% protection on the MIF_{50} with salbutamol.

Exercise induced falls in MIF_{50} and FEV_1 at the screening ECT, after salbutamol and placebo, including their statistical differences are shown in table 2.
The falls in MIF_{50} and FEV_1 separated by intervention per child are shown in figures 2 and 3.

Responders/ non-responders

As can be seen in figure 2, there were 8 responders to treatment with salbutamol against inspiratory flow limitation and 8 non-responders. The median percentage of protection ((% fall placebo - % fall salbutamol) / % fall placebo) of salbutamol against inspiratory flow limitation was 45.6% (IQR 2.9%-73.0%).

The characteristics of responders and non-responders against inspiratory flow limitation are shown in table 3. Characteristics were not significantly different between the responders and non-responders (all p values > 0.62), except for the higher use of leukotriene receptor antagonists in the group of non-responders (p=0.007).

The screening ECT showed 11 children with a combined inspiratory and expiratory flow limitation. These children were analyzed for the relation between the protective effect of salbutamol against an inspiratory flow limitation and EIB.

No correlation was found between the protection of salbutamol against fall in FEV_1 and against fall in MIF_{50} in comparison to placebo (r= 0.21; p = 0.43).

DISCUSSION

We observed an inconsistent, individually variable protection of salbutamol against exercise induced inspiratory flow limitation in contrast to the consistent protective effect of salbutamol against EIB. We confirmed that a substantial number of asthmatic children with exercise induced flow limitation have an inspiratory flow limitation which is independent from EIB.

We observed the same prevalence of exercise induced inspiratory, expiratory and combined flow limitation as other studies investigating flow limitation after airway challenge in asthmatic children and adults.

To our knowledge, this is the first study to analyze the protection of salbutamol against inspiratory flow limitation in asthmatic patients. One study found a significant reduction of metacholine induced inspiratory flow limitation with a combined treatment of nasal corticosteroids, pseudoephedrine and antibiotics in children[8].

Exercise induced hyperventilation dries the airway epithelium and leads to hyperosmolarity of the airway surface fluid, triggering residential mucosal mast cells to release inflammatory mediators such as histamine [1,16]. It is assumed that the bronchoprotective effect of salbutamol in EIB is largely attained by its stabilizing effect on beta 2 receptors on mast cells[1,9]. Exercise also cools the airways, that rapidly rewarm and congest when exercise induced hyperventilation ceases. Both cooling and drying mainly occur in the larger airways. As we only found a mild protective effect of salbutamol against exercise induced inspiratory flow limitation in contrast to the consistent effect on EIB, we speculate that the role of inflammatory mediators is not as important in the pathofysiology of exercise induced inspiratory flow limitation as in EIB. Perhaps rebound rewarming after exercise of the hyperplastic vascular bed present in asthmatic airways can lead to congestion and obstruction of the larger airways leading to an inspiratory flow limitation. Asthma is not in all patients confined to conductive and small airways and possibly the inspiratory flow limitation reflects the presence of airway inflammation in the larger airways. Asthmatic children who experience persistent exercise induced asthmatic symptoms despite the use of (prophylactic) salbutamol, may suffer from an inspiratory

flow limitation as a component of their asthma.
Exercise induced inspiratory flow limitation can be induced by vocal cord dysfunction (VCD). However, the inspiratory flow limitation we observed progressed after ceasing exercise and was not accompanied with acute choking or an inspiratory stridor, which strongly suggests another cause than VCD [17-20]. Moreover VCD is relatively rare in this young age group whilst an inspiratory flow limitation was observed in the majority of children.
In our population 19.4% of the children were not able to perform reliable and duplicated inspiratory flow-volume loops. This is similar to Tomalek et al. et al. who showed that 23% of healthy children in a similar age group could not perform acceptable inspiratory flow-volume loops [21]. According to ERS criteria volume loops need to be repeated to obtain a reliable value.
The main strength of this study is the prospective double-blind placebo-controlled randomized cross-over design. Also, a short time period between the two interventions was pursued (<1 week) and all tests were carried out by the same investigator in standardized air conditions. None of the children quitted the ECT's prematurely.
A limitation of our study is that due to the tight time schedule of obtaining flow volume loops after exercise, not all children were able to perform comparable duplicated inspiratory volume loops. Another limitation is the administration of 200µg salbutamol which could have been a too low dose to result in a clinical effect in all children with exercise induced inspiratory flow limitation.
More research is necessary to analyze the pathophysiological basis of exercise induced inspiratory flow limitation. We suggest a study investigating the protection of inhaled vasoconstrictive agents, such as alpha agonists, against exercise induced flow limitation to evaluate the contribution of vascular phenomena to an exercised induced inspiratory flow limitation and EIB.

CONCLUSIONS

We observed an inconsistent, individually variable protection of salbutamol against exercise induced inspiratory flow limitation in contrast to the consistent protective effect of salbutamol against EIB. We confirmed that a substantial number of asthmatic children with exercise induced flow limitation have an inspiratory flow limitation which is independent from EIB.
Asthmatic children who experience salbutamol resistant exercise induced symptoms may suffer from an inspiratory flow limitation, which can be identified in an ECT with measurement of both in and expiratory flow volume loops.

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Chapter 9

Predicting the effect of long term treatment with BDP by a single dose effect: a pilot study

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SUMMARY

Rationale
Bronchial hyperresponsiveness (BHR) is a key feature of asthma leading to episodic respiratory symptoms. Although inhaled corticosteroids (ICS) reduce BHR, the effect varies between individuals. At present there is a lack of diagnostic tools to identify and assess this individual responsiveness to ICS. Our aim was to investigate the relation between the acute effect of a single dose of beclomethasone dipropionate (BDP) on BHR to mannitol PD_{15} and the effect after 4 weeks of treatment with BDP.

Methods
Twelve steroid naïve children aged 12-18 years with mild to moderate asthma and symptoms of exercise induced bronchoconstriction (EIB) who started treatment with BDP were studied in this prospective, open label study. Children performed a baseline mannitol challenge and within one week a second mannitol challenge 6 hours after a single inhaled dose of 200µg BDP. After 4 weeks of twice daily treatment with 200µg BDP, a third mannitol challenge was performed 24 hours after the last dose of BDP. The change in the threshold dose of mannitol that provoked a $\geq$ 15% fall in FEV_1 was calculated and the correlation between the change after a single dose and after 4 weeks of treatment with BDP was analyzed.

Results
Ten out of twelve children finished the study. Six out of these ten children showed a reduction in mannitol responsiveness after a single dose of BDP demonstrated by an increase in threshold dose of 1 or more steps. Four children showed no reduction in responsiveness either acutely or after 4 weeks treatment. The change in mannitol responsiveness after a single dose BDP and after 4 weeks BDP treatment was highly correlated (intra class correlation 0.879).

Conclusion
The benefit of 4 weeks of ICS treatment can be predicted by the acute change in mannitol responsiveness 6 hours after a single dose of ICS.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways featured by bronchial hyperresponsiveness (BHR) to various triggers. Exercise is a common trigger in childhood asthma and children report it as the worst aspect of their asthma. Asthma treatment is standardized, however clinical phenotypes differ exemplified by the variability of patients' responses to medications [1-4]. No asthma medication currently available provides benefit to all patients urging the need for personalized treatment.

Inhaled corticosteroids (ICS) reduce airway inflammation and are the mainstay of controller therapy in children with asthma [5]. However, beclomethasone dipropionate (BDP) for 4 weeks only provided significant protection against exercise induced bronchoconstriction (EIB) in 44% of asthmatic children[1]. A high single dose of ICS provides acute protection against BHR but also shows a variability as observed with longer term treatment [6-10].

A mannitol challenge test is a sensitive, valid test assessing indirect BHR and is highly related to EIB [11]. A mannitol challenge is an appropriate tool to monitor the effects of ICS in childhood asthma [12].

A challenge test with mannitol is preferable to tests with direct stimuli, such as histamine and methacholine, when investigating the effect of asthma controller drugs, as BHR to indirect stimuli reflects BHR to daily occurring triggers and airway inflammation [13].

It is a critical clinical question whether a particular therapy will be effective in an individual child with symptoms of asthma. At the moment there is a lack of diagnostic tools assessing this individual responsiveness that could aid clinical decision making and prevent inappropriate long term therapy.

We proposed that the effect of a single dose of inhaled BDP on mannitol responsiveness could predict the effect of longer term therapy with BDP.

The aim of our study was to investigate the relation between the change in mannitol PD_{15} (provoking dose of mannitol to cause a ≥ 15% fall in FEV_1) 6 hours after a single dose of BDP and after 4 weeks of standard treatment with BDP.

METHODS

Patients

In this prospective open labeled study we assessed the predictive value of the acute effect of BDP on a mannitol challenge test for the outcome of 4 weeks treatment with BDP. Children aged 12-18 years with a history of mild to moderate asthma who were steroid naïve and started on BDP for clinical reasons were recruited from the pediatric outpatient clinic of the Medisch Spectrum Twente (MST) Enschede, the Netherlands. Children with a baseline FEV_1 < 70% of predicted value were excluded, as well as children using systemic corticosteroids, antihistamines or anticholinergics two weeks prior to the study. Deviation of the FEV_1 before the subsequent mannitol challenges of more than 12 % from baseline FEV_1 at the first mannitol challenge test led to exclusion as well.

Mannitol challenges

Children performed three mannitol challenges with lung function measurements before, during and after the challenge according to Kersten et al.[11].

A fall of ≥15% in FEV_1 from baseline was considered a positive response and the dose at which this occurred the threshold dose. The test ended when such a fall occurred or the cumulative dose of 635 mg mannitol had been administered. A decrease in responsiveness to mannitol was identified by the change from baseline, in the threshold dose of mannitol that provoked a ≥ 15% fall in FEV_1. The correlation between the change in the threshold dose after a single treatment and after 4 weeks of treatment with BDP was analyzed. In addition the actual provoking dose to cause a 15% fall in FEV_1 (PD_{15}) was calculated.

Children were neither allowed to perform vigorous exercise nor to consume caffeine containing foods or drinks for 8 hours before the mannitol challenges. Children received a dose of inhaled salbutamol 100µg if their FEV_1 fell ≥ 15% after a mannitol challenge. They received a second dose of salbutamol 100µg if their FEV_1 did not recover within 95% of baseline after 10 minutes.

A MicroLoop® spirometer, in combination with Spida5® software, was used to measure pulmonary volumes and flow-volume loops.

Beclomethasone treatment

At the baseline visit children received a prescription for 4 weeks treatment with a therapeutic dose of BDP. Within a week after the baseline visit children started on a therapeutic dose of 400µg/day of BDP from a metered dose inhaler. Six hours after the first dose of 200µg, a second mannitol challenge was performed (14:00h p.m.). After 4 weeks of treatment a third mannitol challenge was performed. The last BDP dose was inhaled 24 hours before the mannitol challenge.

Sample size calculation

No sample size calculation was performed, because this study was deemed a pilot study. This study was conducted between July 2010 and October 2012. Results were analyzed after the inclusion of 12 children.

Statistical analyses

Best values of spirometric measurements were used for statistical calculations. Results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (minimum; maximum) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal. Normality of data was visually inspected. Within person changes in continuous variables (e.g. fall in FEV_1) were analyzed with a paired T-test or a Wilcoxon signed rank test, as appropriate.

Intra class correlation was used to assess the correlation between the acute change in mannitol responsiveness 6 hours after a single dose of BDP and after 4 weeks of BDP treatment. To analyze a positive predicted value a linear regression test was used. A 2 sided value of $P < 0.05$ was considered statistically significant. Data was analyzed with SPSS® for Windows® version 21 (IBM, Chicago, IL, USA) analytical software.

Table 1: Baseline characteristics of study group

Number of patients	12
Age (years)	13.6 ± 1.5
Boys	4 (33.3%)
Duration of asthma (years)	0.92 (0.08-4.5)
LTRA's >3 months	1 (8.3)
Nasal corticosteroids >3 months	3 (25)
FEV_1 % predicted[a]	80.0 (73.4-94.4)
Threshold dose of mannitol for 15% fall at baseline (mg)	155 (75-315)
Allergy	
- Proven	7 (58.3)
- Unknown	3 (25)

Data expressed as mean values ± standard deviation, median with interquartile ranges or numbers (percentage). LTRA's: leukotriene antagonists; [a] FEV_1: forced expiratory volume in 1sec, percentage of predicted based on the reference values of Koopman et al[14]; Allergy: proven by radioallergosorbent test or skin prick test.

Ethical Considerations

This study was approved by the hospital ethics review board. All children and parents/guardians received written patient information and provided written informed consent to participate in this study.

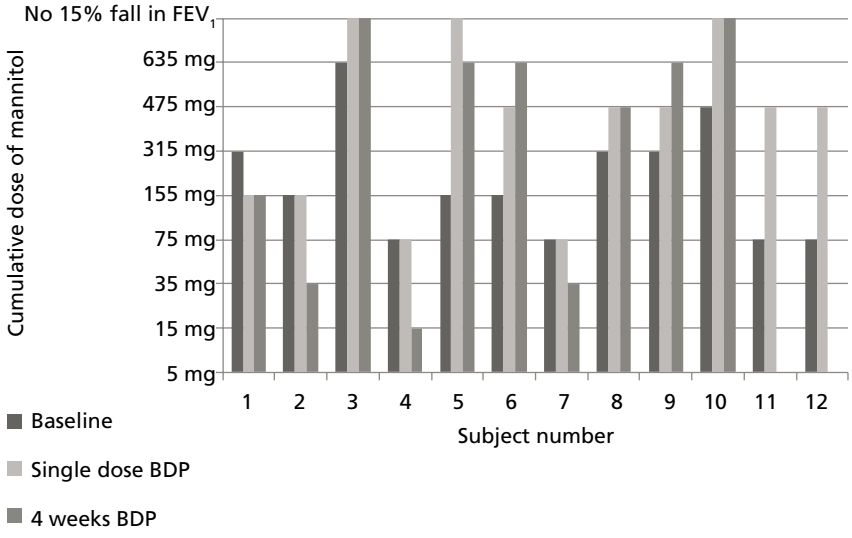

Figure 1. Change in mannitol threshold after a single dose BDP and 4 weeks of BDP treatment. BDP: beclomethasone dipropionate.

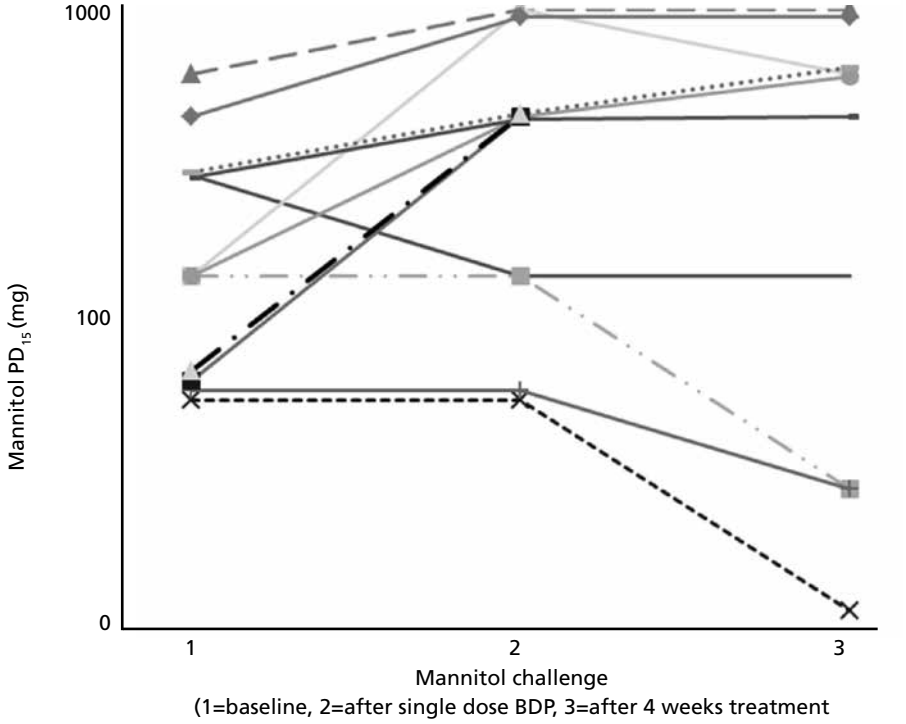

Figure 2. Mannitol PD_{15} for each individual child. PD_{15}: provoking dose of mannitol to cause a ≥ 15% fall in FEV[1]

RESULTS

Twelve children entered the study (4 boys, mean age 13.6 ± 1.5, range 12-17); two children did not finish the third test; one did not want to proceed because of emotional lability, one quitted her BDP treatment after five days because of headache complaints.

Baseline characteristics of the 12 included children are shown in table 1.

Median FEV_1 as a percentage of predicted was 80.0% (IQR 73.4-94.4%) and median mannitol responsiveness was 155 mg (IQR 75-315 mg). No children showed a decline in asthma control as assessed with FEV_1% predicted at the second visit.

The individual data for the threshold dose of mannitol that caused ≥15% fall in FEV_1 are illustrated in Figure 1. The actual PD_{15} for each child for each of the three mannitol challenges are illustrated in Figure 2 and show the consistency in either the benefit or no benefit between the 2nd and 3rd visit. The FEV_1 as a % of predicted per individual child prior to each of the three mannitol challenges is illustrated in Figure 3.

There were 4 children (Subjects 1, 2, 4 & 7) who showed no reduction in mannitol responsiveness after a single dose of BDP. These 4 also did not have a reduction in mannitol responsiveness at the third test after 4 weeks of treatment (Figure 4).

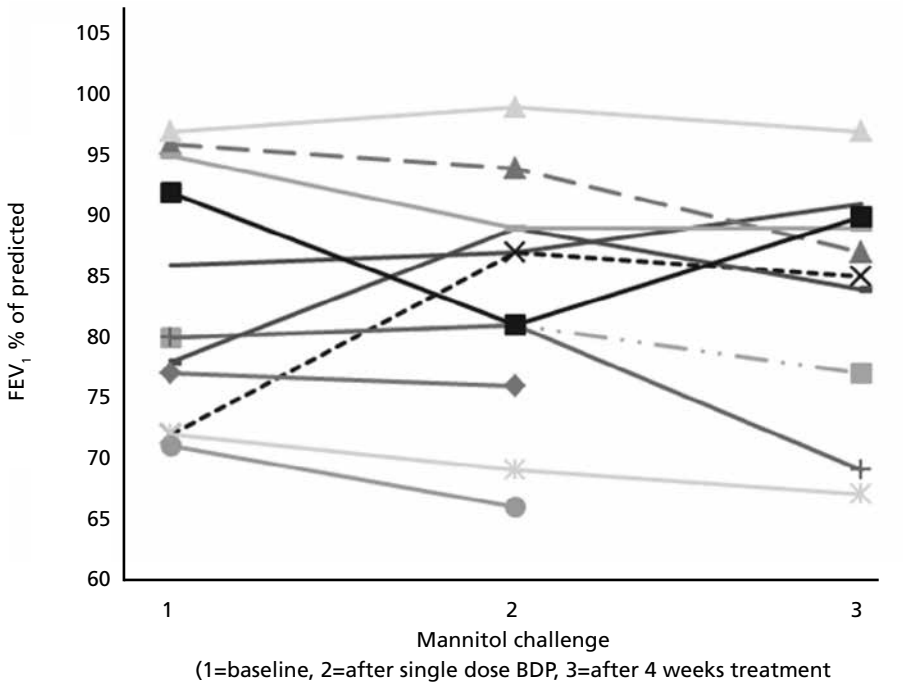

Figure 3. FEV_1 as % of predicted for each individual child

The other 8 children showed a reduction in mannitol responsiveness after a single dose of BDP compared to baseline. (Figure 4) Six (Subjects 3, 5, 6, 8, 9, 10) of these 8 children completed the third test and all 6 also showed a reduction in mannitol responsiveness after 4 weeks of treatment with BDP.

DISCUSSION

In this pilot study we showed that the effect of a single dose of inhaled BDP on mannitol responsiveness can predict the effect of 4 weeks treatment with BDP in steroid naïve asthmatic children.

To our knowledge, this is the first study investigating the relation between the mannitol responsiveness to a single inhaled dose of BDP and the change in mannitol responsiveness after 4 weeks of twice daily BDP treatment.

Eight out of twelve children showed a reduction in mannitol responsiveness after a single low dose of 200µg BDP. Previous studies showed a similar significant but variable effect of a single dose ICS against indirect BHR in asthmatic children and adults[6-10]. Thio et al. showed that there was a large individual variability in the protection against EIB of a single dose of ICS with 4 out of 9 children showing no effect from a single high dose of ICS[6].

We found that 4 out of 12 children did not show a response to a single dose of inhaled BDP. All 4 of these children did not show a decrease in mannitol respon-

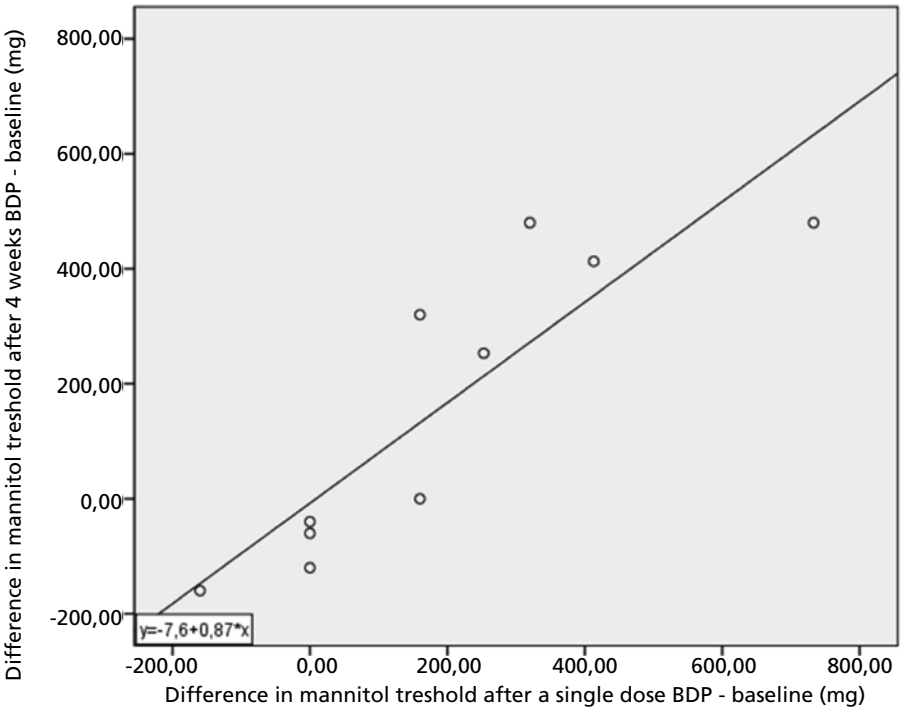

Figure 4. Correlation between the change in the threshold dose to induce 15% fall in FEV_1 between baseline and after a single dose of 200µg of inhaled BDP and between baseline and after 4 weeks of twice daily 200µg BDP treatment (n=10)

siveness after 4 weeks either. This corresponds to previous studies that have shown that not all children benefit from regular treatment with ICS[1-4].

Predicting the individual response to ICS is of clinical relevance. Change in mannitol responsiveness after a single dose of ICS could provide objective information predicting the efficacy of long term regular treatment. Long term therapy with a standardized dose of ICS is started in every child with mild or moderate asthma according to current guidelines, but clinical evaluation of therapeutic effects can be difficult as it is largely based on medical history which is notoriously unreliable. This may lead to inappropriately stepping up or stopping of therapy[5]. Testing the response to a single dose of ICS before treatment could be a diagnostic option to identify children who are hypo-responsive to a regular dose of ICS and could be considered for an alternative treatment strategy. The benefit was observed simply by using the change in threshold dose of mannitol making it simple to measure and report. The benefit was unlikely to be accounted for by a significant increase in FEV_1 in response to treatment as this occurred in only 2 of the 8 subjects.

Strengths of this pilot study include the prospective design and the short duration of the study period per child. Limitations include the small sample of children and the absence of measuring adherence. However in a previous study analyzing the adherence in our population of asthmatic children who were enrolled in our com-

prehensive asthma program median adherence was 83% [15]. A second possible confounder was the lack of a placebo arm. However, the study was designed to correlate the single dose response of BDP to the response of regular daily treatment with BDP. A third factor may be the duration of the 24 hours interval after the last dose of BDP of the 4 weeks treatment. We chose to schedule the last BDP dose to be inhaled 24 hours before the mannitol challenge to separate the acute from the long term response. Luijk et al. showed that the effect of a single inhaled dose of 1.0 mg fluticasone propionate on an indirect challenge with adenosine-5-monophosphate had waned 26 hours after dosing[7]. Two children did not perform the third mannitol test, one because he refused to finish the test. In our experience children, especially young children, can be reluctant to complete a mannitol test.

Further studies with larger study populations are needed to confirm our results.

The change of mannitol responsiveness after a single dose of BDP can predict the effect of 4 weeks of treatment in steroid naïve asthmatic children. Measuring the mannitol responsiveness after the acute administration of a single dose of ICS may provide a useful tool for the clinician to guide the start of ICS therapy.

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Chapter 10

General discussion

GENERAL DISCUSSION

In this thesis we investigated various aspects of inhalation treatment in asthmatic children. New insights into the how, when and why regarding the use of inhalation therapy were studied and discussed. Inhalation medication is a topical treatment and the preferred route for the treatment of asthma as it administrates the medication directly on the inflamed mucosa, maximizing the effect and minimizing the side effects. Inhalation treatment can be used in both the diagnostic and therapeutic field. Also, we confirmed the jumping castle to be an appropriate format for an exercise challenge test in young asthmatic children (4-8 years old), which is in line with a previous study [1].
Many asthmatic children still have symptoms despite the prescription of appropriately inhaled medication. Non-adherence (intentional or unintentional) to medical treatment, incorrect use of devices, inter-individual variability in response to medical treatment and a partly unknown pathophysiology of asthma are important causes of treatment failure.

Adherence and inhalation technique

Non-adherence has a detrimental influence on the efficacy of medical treatment of asthma [2-4]. Based on the literature, adherence is around 40-60% in asthmatic children [5]. A distinction can be made between unintentional and intentional non-adherence. Unintentional non-adherence is related to barriers to achieve adherence, such as limited family routines and child raising issues. Intentional non-adherence refers to situations where patients deliberately choose not to follow the doctor's recommendations, based on their own illness perceptions and medication beliefs. Such perceptions and beliefs have consistently been shown to be strong determinants of adherence [6,7]. Our hypothesis was that discussing an asthma challenge test result with parents, could have a significant impact on the awareness of their child's symptoms and therefore on adherence. We discussed the result of an exercise challenge test (ECT) directly after the ECT, which is highly specific for asthma. We showed a high median adherence of 83% of the children in our outpatient asthma program and no clinical relevant change in adherence after the ECT, irrespective of the presence of exercise induced bronchoconstriction (EIB) and baseline adherence. Medication beliefs of most parents (82.1%) reflected perceptions about necessity of medical treatment that outweighed their concerns and showed no clinical relevant change after the ECT, implicating low intentional non-adherence. We did not observe the phenomenon of medication dumping. Probably, our high baseline adherence precluded an improvement in adherence. However, also the children with a poor adherence at baseline (<80%) did not show an improvement. Another explanation could be that, because of our comprehensive asthma care program, the majority of parents did not show intentional non-adherence opinions as suggested in the positive necessity-concern ratios measured with our beliefs about medicines questionnaire (BMQ). We observed similar scores of BMQ items in children with a high and low adherence. This suggests that they experienced barriers to improvement that are difficult to influence by discussing ECT results (unintentional non-adherence). This is in line with the results of Klok et al. who showed that in a study population with a high adherence, especially family

related barriers are the cause of unintentional non-adherence, for example child raising issues or missing family routines [7]. We speculate that without a comprehensive asthma care program and thus more children with intentional non-adherence, the improvement in adherence could have been more pronounced. Future research should be directed to investigate the effect of discussing an ECT result with parents of asthmatic children with a high intentional non-adherence, as possibly can be found in newly referred children.

Correct use of inhalation devices is a prerequisite for successful drug treatment of asthma and errors in inhalation technique are associated with poor asthma control [8-11]. Unfortunately, inhaler technique is inadequate in many asthmatic children: even after inhalation instruction many children use their inhalers devices too poorly to result in reliable drug delivery [10,12,13].

Current international guidelines recommend repeated comprehensive inhalation instructions every three to six months to improve inhalation technique [12,14]. The results of our study demonstrated that six weeks after a single inhalation instruction significantly more asthmatic children (69.7% vs. 36.3%) performed a perfect inhalation technique. However, of those who did not perform a perfect technique significantly more children made an essential error, with failing to shake their inhaler being the main error (6.6% at baseline, 16.9% six weeks after the single instruction). For suspension formulations, shaking the inhaler before actuation is important, since omitting shaking will affect the dose uniformity. Not shaking the inhaler reduces the delivered dose of the pressurized metered dose inhaler with spacer device (pMDI/s) with approximately 50% [15]. Kamps et al. showed in a similar study that with at least two consecutive instructions in a four week period 93% of the children performed all essential steps correctly when reviewed six weeks after the last instruction [12]. However, in daily clinical practice this seems to be too great a burden for patients and health care providers.

Children in our study showed few essential errors in inhalation technique at baseline (8.8%) compared to 16-40% in other studies among outpatient children using a pMDI/s [12,16-18]. In line with other studies, we observed that failing to shake the inhaler was the most frequent essential error at baseline (6.6%). In the studies of Kamps at al. 19.6% of clinical outpatients and 29% of newly referred children failed to shake their inhaler [12,18]. We hypothesize that the low number of essential errors in our study group compared to other studies is a consequence of the organization of our asthma care. In our clinic, comprehensive asthma management consists of frequent follow up visits every four months alternately to a pediatrician and a dedicated asthma nurse who extensively checks inhalation technique.

We were surprised to find more children failing to shake their inhaler six weeks after inhalation instruction resulting in a decline of 91% to 83% of children who carried out all essential steps (i.e. shake the inhaler) correctly. We speculate that focusing on other errors induced this increase in failing to shake the inhaler. This shows that reinforcement of shaking the inhaler, even if performed correctly previously, should be highly emphasized, since omitting shaking can reduce the delivered dose of the pMDI/s with approximately 35%.

According to our observations the recommended interval of 3-6 months to monitor inhalation technique is too long to prevent the appearance of new essential errors. We recommend to re-evaluate inhaler technique more frequently than ac-

cording to current guidelines. To further explore inhalation technique and adherence in daily life at home, future studies could use modern internet technology as a tool. Inhalation technique can be monitored at home, for example with an iPad, and evaluated by health care providers.

Body posture

A drawback of popular devices as the breath actuated inhaler (BAI) is the massive impaction (40-60%) of medication in the upper airway, resulting in local side effects as coughing, hoarseness, dysphonia, and oral candidiasis [19,20]. Recently, Brandao et al. showed that inhaling nebulized bronchodilators in a forward leaning body posture during an asthma exacerbation accelerated recovery of lung function in asthmatic adults compared to the conventional body posture [21]. This suggests that body posture during inhalation can influence effects of inhaled medication, possibly by a change in pulmonary deposition. We hypothesized that this phenomenon could be even more relevant in asthmatic children as they have a smaller upper airway compared to adults.

We showed in a pilot study of 42 children inhaling salbutamol with a BAI either in the standard or in the forward leaning body posture with the neck extended, that a forward leaning body posture resulted in significant more reversibility of FEV_1 and MEF_{75}. This is in line with the findings of Brandao et al [21]. A limitation of our study was the fact that children, who were scheduled for a routine reversibility lung function, alternately inhaled in the standard or the forward body posture and were not randomized. Children inhaling in the standard body posture showed a non significant higher baseline FEV_1 which left less room for improvement in this group compared to the forward leaning body posture group. An additional limitation was that the pulmonary function technician, although he or she was different from the administrator of the inhaled medication, was not blinded to body posture during inhalation. These limitations could have resulted in bias; however, we regarded the observed differences as clinically relevant.

These results led us to design a randomized controlled, single blind, cross-over trial, in which children performed four times a spirometry, two times with inhaling 200µg salbutamol and two times with inhaling 400µg salbutamol with a BAI. Both doses were inhaled once in the standard body posture and once in the forward leaning body posture. We showed that inhalation of 400µg salbutamol resulted in a significantly higher reversibility of FEV_1 compared to inhaling 200µg salbutamol. On the other hand, inhaling in a forward leaning posture did not increase reversibility of spirometric parameters compared to the standard posture in asthmatic children. Our results are conflicting with the study of Brandao et al. and our pilot study, possibly because we used a BAI with particles with a small mass median diameter of the droplets. Stretching the upper airway may have a higher impact when inhaling large particles from nebulized bronchodilators as in the study of Brandao et al. Another possible reason for the discrepancy between our observations and Brandao's study is patient selection. Brandao studied adults during an asthma exacerbation in contrast to our study that investigated clinically stable asthmatic children. During an asthma attack there is a different breathing pattern with a tachypnoe resulting in higher flow rates in the upper airway. Stretching the

upper airway may counteract the oropharyngeal impaction of medication. Another explanation may be that Brandao nebulized the patients for ten minutes in the forward leaning posture, implicating breathing in this specific posture, which may have speeded the rate of recovery of lung function as well. A forward leaning posture shifts the center of gravity and optimizes expiration. A possible explanation for the contrasting results between this study and our pilot study could be the imbalance in baseline lung function in the pilot study as described above. A future study should investigate the clinical effect of a forward leaning posture during inhalation of salbutamol in children during an asthma attack and the effect of dry powder devices with larger particles in the forward leaning body posture. We recommend to administer 400 µg instead of 200 µg salbutamol with a BAI in reversibility measurements, since inhalation of 400 µg showed significantly greater reversibility compared to inhalation of 200µg salbutamol.

Finally, we performed a study that investigated the protective effect against EIB of a single dose of 200µg beclomethasone dipropionate (BDP) inhaled in a forward leaning body posture, compared to the standard posture, four hours prior to an ECT in steroid naïve children i.e. children who do not use maintenance inhaled corticosteroids (ICS). We also evaluated the bronchodilating effect of a single dose of BDP in the forward leaning versus standard posture. The inhalation of a single dose of BDP in both body postures had a similar protective effect against EIB in asthmatic children, and was of similar magnitude compared to previous studies using a high single dose of ICS of 1000-1600µg [22-25]. Apparently, the effect of a single dose of 200µg BDP inhaled in the standard posture was already on the flat upper part of the dose response curve precluding to find a difference between both body postures. We observed a, small but significant, stronger bronchodilating effect of inhaling 200µg BDP in the forward leaning posture compared to inhaling in the standard posture. Previous studies found a similar acute bronchodilating effect with a high single dose of ICS (1000-1600µg) inhaled in a standard posture in steroid naïve asthmatic children and adults [26-29].

Inhaling a single dose of BDP in the forward leaning posture significantly delayed the fall in FEV_1 from 1.5 minute to 2.5 minutes after exercise, which is clinically beneficial for children during play and interval sports. Studies have shown that EIB in children starts earlier after and frequently during exercise (breakthrough asthma) compared to adults, which is detrimental for participation in play and sports [1]. Resuming exercise before the maximum fall in FEV_1 occurs reverses the fall. Thus, a delayed maximum fall in FEV_1 buys children time, which can preclude them from dropping out [30,31].

The protective effect of a single dose of ICS in asthmatic children on EIB is probably mediated by the acute vasoconstrictive effect of ICS on the hypertrophied and hyperplastic capillary bed, which is resident in the inflamed airways of asthmatics. Airway wall swelling does contribute substantially to EIB [25]. Kippelen et al. showed that a single dose of BDP also blocked the release of mast cell mediators, such as prostaglandin D2, leading to reduced airway narrowing [23].

A future study should investigate the effect of inhaling a lower dose of BDP (100µg) in a forward leaning posture on EIB, aiming to be on the steep part of the dose response curve, and also in children already who use maintenance ICS.

New insights in the diagnostic and therapeutic use of medication

An ECT can detect EIB, diagnose asthma and evaluate asthma treatment [32]. Daily use of ICS reduces EIB in asthmatic children. Thio et al. showed that a high single dose inhaled four hours prior to an ECT also provided protection against EIB in steroid naïve asthmatic children [25], while we observed that a low single dose of 200µg BDP provided ≥50% protection against EIB in the majority of steroid naïve asthmatic children as well. However, there was a considerable variability in the protection against EIB, with a trend towards more boys being non-responders. Other studies also showed an acute protection of ICS against bronchial hyperresponsiveness to indirect stimuli but used high doses of 1000-1600µg ICS inhaled four to eight hours before a challenge in adult asthmatics [22,23]. Kippelen et al. demonstrated that a high dose of 1500µg BDP provided significant protection against BHR as assessed by eucapnic voluntary hyperventilation in both untrained adult asthmatics and athletes with EIB [23]. The acute protective effect of a low single dose ICS against EIB may be clinically beneficial for mild asthmatic children who have EIB, but do not require maintenance ICS therapy. Although stronger, bronchoprotection of salbutamol against EIB is short lived with a maximum of two hours, and subject to tachyphylaxis [33-35]. Since topical steroids have a potent vasoconstrictive effect, the protective effect of a single inhaled dose of BDP against EIB suggests that bronchovascular engorgement does play a substantial role in the pathophysiology of EIB. The variability of the response to BDP observed in our study suggests that the relative contribution of vascular engorgement and mucosal edema to airway obstruction may vary from person to person underlining the heterogeneity of asthma in childhood. We were surprised to find a trend towards more boys in the non-responder group, which may be due to smaller airways of prepuberal boys compared to girls [36]. In eight children we found severe EIB (fall in $FEV_{0.5}$ or $FEV_1 \geq$ 50%), which is not compatible with mild asthma and does reflect marked airway inflammation. These children were started on maintenance ICS after the study. The acute response of a single dose of ICS in asthmatic children may have implications for guidelines relating to medication restrictions before bronchoprovocative tests. Currently there are no restrictions for the use of inhaled corticosteroids before lung function tests. Further dose response studies including different time points after single dosing of ICS in asthmatic children with or without maintenance ICS could provide data about the sustained effect of a single dose ICS on lung function tests. Further studies could also investigate whether asthmatic children with EIB, without other symptoms of asthma, could profit from the acute effect of a low single dose ICS in the morning.

Recent studies have shown that an exercise challenge test not only can induce EIB but also can induce inspiratory flow limitation [37-41]. Exercise induced inspiratory flow limitation is independent from EIB and also occurs after exercise. It is a clinically different entity than vocal cord dysfunction (VCD), which is accompanied by acute inspiratory stridor during exercise [37-40]. Inspiratory flow limitation is defined as a fall in mid inspiratory flow (MIF_{50}) of more than 25% [37,39,40]. Exercise induces the release of mediators from inflammatory cells resident in the airway mucosa. These mediators are responsible for bronchial narrowing by activation of the inflammatory response in the asthmatic airway. Inhaled salbutamol stabilizes inflammatory

cells and can therefore provide excellent protection [42,43]. The pathophysiology of exercise induced inspiratory flow limitation is unknown but inflammatory mediators released may be directly or indirectly involved. Our prospective double blind, placebo-controlled cross-over study demonstrated that salbutamol offered a significant but inconsistent, individually variable protection against exercise induced inspiratory flow limitation in contrast to the consistent protective effect against EIB. We observed the same prevalence of exercise induced inspiratory, expiratory and combined flow limitation as other studies investigating flow limitation after airway challenge in asthmatic children and adults [37,38,40,42]. The protective effect of salbutamol against exercise induced inspiratory flow limitation was not related to the protective effect against EIB. Exercise induced hyperventilation dries the airway epithelium and leads to hyperosmolarity of the airway surface fluid, triggering residential mucosal mast cells to release inflammatory mediators such as histamine [42,44]. It is assumed that the bronchoprotective effect of salbutamol in EIB is largely attained by its stabilizing effect on beta 2 receptors on mast cells [42,43]. Exercise also cools the airways, which rapidly re-heat and congest when exercise induced hyperventilation ceases. Both cooling and drying mainly occur in the conductive airways. As we found only a mild protective effect of salbutamol against exercise induced inspiratory flow limitation in contrast to the consistent effect on EIB, we speculate that the role of inflammatory mediators is not as important in the pathophysiology of exercise induced inspiratory flow limitation as in EIB. Perhaps rebound reheating after exercise of the hyperplastic vascular bed present in asthmatics can lead to congestion and obstruction of the larger airways leading to an inspiratory flow limitation. Asthma is not in all patients confined to small airways and possibly the inspiratory flow limitation reflects the presence of airway inflammation in the larger airways. Exercise induced inspiratory flow limitation can be induced by vocal cord dysfunction (VCD). However, the inspiratory flow limitation we observed progressed and peaked after ceasing exercise and was not accompanied with acute choking or an inspiratory stridor, which strongly suggests another cause than VCD [45-48]. Moreover VCD is relatively rare in this young age group whilst an inspiratory flow limitation was observed in the majority of children.

Asthmatic children who experience salbutamol resistant exercise induced symptoms may suffer from an inspiratory flow limitation, which can be identified in an ECT with measurement of both in and expiratory flow volume loops. More research is necessary to analyze the pathophysiological basis of exercise induced inspiratory flow limitation. We suggest a study investigating the protection of inhaled vasoconstrictive agents, such as alpha agonists, against exercise induced flow limitation to evaluate the contribution of vascular phenomena to an exercised induced inspiratory flow limitation and EIB.

Our final study was a pilot study investigating the relationship between the protective effect of a single dose of ICS and four weeks treatment with ICS against bronchial hyperresponsiveness to mannitol in asthmatic children. It is well known that clinical asthma phenotypes differ, exemplified by the variability of patients' responses to medications [49-52]. No single asthma medication currently available provides benefit to all patients urging the need for personalized treatment. It is a critical clinical question whether a particular therapy will be effective in an

individual child with symptoms of asthma. At present there is a lack of diagnostic tools assessing this individual responsiveness that could aid clinical decision making and prevent inappropriate long term therapy.
A single dose of ICS provides acute protection against BHR however there is a variable response similar as observed with longer term treatment [22-25,53]. A mannitol challenge test is a sensitive, valid test assessing indirect BHR and is highly related to EIB and can be used to monitor the effects of ICS in asthmatic children over 12 years [54]. We showed that the effect of a single dose of inhaled BDP on mannitol responsiveness is related to the effect of four weeks of treatment with BDP in steroid naïve asthmatic children. Eight out of twelve children showed a reduction in mannitol responsiveness after a single low dose of 200µg BDP. Four out of twelve children (33%) however did not show a response to a single dose of BDP and did not achieve a decrease in mannitol responsiveness after four weeks either. This corresponds to previous studies that have shown that not all children benefit from regular treatment with ICS [49-52]. Assessing the individual response to ICS is of high clinical relevance. Change in mannitol responsiveness after a single dose of ICS could provide objective information predicting the effectiveness of long term regular treatment. Long term therapy with a standardized dose of ICS is started in every child with mild or moderate asthma according to current guidelines, but clinical evaluation of therapeutic effects can be difficult and may lead to inappropriately stepping up or stopping the therapy [55]. Testing the response to a single dose of ICS before treatment could be a diagnostic option to identify children who are hypo-responsive to a regular dose of ICS and could be considered for an alternative treatment strategy. Further studies with larger study populations are needed to confirm our results.

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Chapter 11

Summary

OPTIMIZING INHALATION THERAPY IN CHILDHOOD ASTHMA

Childhood asthma is a common chronic disease, featured by inflammation of the airways and episodic bronchoconstriction. Exercise is an important trigger for bronchoconstriction in asthmatic children. They experience this symptom, limiting participation in play and sports, as the most bothersome aspect of their asthma. Symptoms of exercise induced bronchoconstriction (EIB) can be subtle and stay unrecognized by caregivers and parents, compromising social and motor development. Asthmatic children may adapt to their exercise limitations and avoid symptoms. An exercise challenge test (ECT), especially in cold dry air, can objectify asthmatic symptoms and can be used for diagnosing and monitoring asthma. A cornerstone in asthma treatment is inhalation medication. In this thesis we investigated various aspects of inhalation therapy in childhood asthma with the aim of optimizing this therapy. An introduction to the current state of affairs is to be found in **chapter 1.**

Many asthmatic children don't achieve well controlled asthma, mostly due to suboptimal adherence to medication. Previous studies show a mean adherence of approximately 60% to inhaled medication in asthmatic children. One of the reasons for non-adherence is that patients and their parents do not understand the rationale for treatment. Although this can be overcome by providing appropriate information, studies consistently show that only education is insufficient to improve adherence, indicating that other factors are more important in driving non-adherence. A distinction can be made between unintentional and intentional non-adherence. Unintentional non-adherence is related to barriers to achieve adherence such as limited family routines and child raising issues. Intentional non-adherence refers to patients who deliberately choose not to follow the doctor's recommendations, based on their own illness perceptions and medication beliefs. Such perceptions and beliefs have consistently been shown to be strong determinants of adherence. For example, parents may overestimate disease control because they do not recognize symptoms belonging to their child's disease, which may diminish their perception of the need of daily inhaled corticosteroid (ICS) use.

EIB is one such symptom, which is frequently not recognized by caregivers (especially in young children), as symptoms may be subtle and children do not report them. An ECT is a diagnostic and monitoring tool for asthma, but also offers an opportunity for educating parents about the symptoms of their child. When parents attend their child's ECT and the test result is discussed with them, they may become more aware of these symptoms, and start to realize their child's limitations in play and sports. In **chapter 2** we describe a study that investigated the effects of discussing ECT results with parents on adherence to inhaled maintenance medication and on parental illness perceptions and medication beliefs. We hypothesized that demonstrating EIB in a child may change parental perceptions about the need to use ICS and increase adherence. Children aged four to seven years, with a pediatrician's diagnosis of asthma, performed an ECT at an indoor ice skating rink and the results were discussed with the parents. Adherence was measured from six weeks before until six weeks after the ECT by validated electronic medication loggers. Parents and children also

filled in questionnaires regarding illness perceptions and medication beliefs six weeks before the ECT, immediately after the ECT and six weeks after the ECT. The median baseline adherence was high (83%) and showed no clinical relevant change after the ECT. There was no significant difference in the decrease in adherence between the children with or without EIB. Both children with good adherence (≥80%) and poor adherence (<80%) showed no clinical relevant change in adherence after the ECT. Most parents (81%) showed a positive necessity-concern ratio at baseline, as measured with the Beliefs about Medicines Questionnaire (BMQ). There was no clinical relevant change in medication concerns and necessity scores or in illness perceptions after the ECT. Probably our high baseline adherence (83%) and the fact that most parents demonstrated a positive necessity-concern ratio, implicating low intentional non-adherence, precluded an improvement in adherence after feedback on the ECT. Probably, our already existing comprehensive asthma care program had convinced most parents of the daily use of ICS. Future research should be directed to investigate the effect of discussing ECT results with parents of children with a high intentional non-adherence.

ICS are the cornerstone of treatment for persistent childhood asthma due to their potent anti-inflammatory effects. Correct use of inhalation devices is a prerequisite for successful drug treatment of asthma and errors in inhalation technique are associated with poor asthma control. Unfortunately inhaler technique is inadequate in many asthmatic children: even after inhalation instruction many children use their inhalers devices too poorly to result in reliable drug delivery. **Chapter 3** describes a study evaluating inhalation technique with a pressurised metered dose inhaler with a spacer device (pMDI/s), six weeks after a single instruction, in young asthmatic children who are regularly reviewed by a pediatrician. We also studied the relationship between educational level of parents and inhalation technique of their child.

Ninety-one children aged four to eight years were asked to demonstrate their habitual inhalation technique with or without parental supervision, according to their home situation. Errors in inhalation technique were scored on an inhaler specific checklist, designed by the Dutch Lung Foundation. Immediately after the review of the inhalation technique a tailored instruction was provided. Six weeks later the inhalation technique was reviewed again and significantly more children showed a perfect inhalation technique (68.5% versus 36.3% p=<0.001). However, significantly more children made the essential error of failing to shake their inhaler before use (16.9% versus 6.6%, p=0.035). Inhalation technique of the child was not associated with educational level of the parents. We recommend to re-evaluate inhaler technique more frequently than according to current guidelines. In addition, reinforcement on essential steps such as shaking the inhaler that were performed correctly previously should be emphasized, as well as the reason for shaking.

Deposition of inhaled medication in the upper airways can compromize deposition at the target area. This upper airway deposition is partially caused by the sharp angle between the pharynx and trachea. Even with an optimal inhalation technique with a breath actuated inhaler 50-60% of the dose of beclomethasone dipropionate (BDP) impacted in the oropharynx in children under the age of 12, as measured in a radio-labeled study. The aim of the study described in **chapter 4**

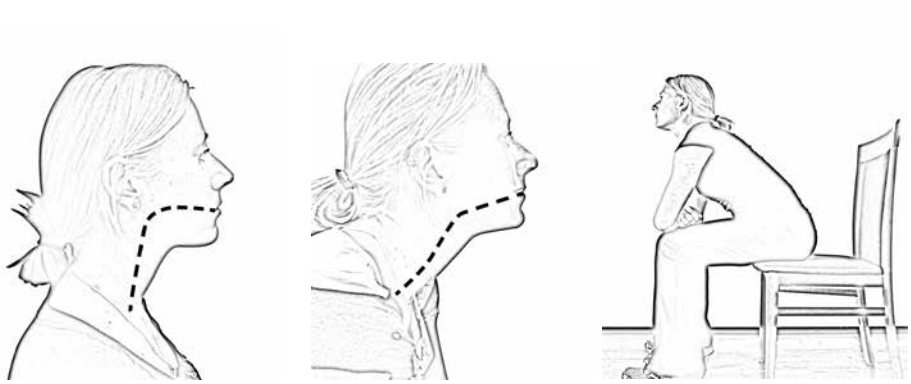


Figure 1 Standard and forward leaning body posture. 90° bent airway in standard body posture (left); stretched airway in forward leaning body posture with the neck extended ("sniffing" position) (middle); forward leaning body posture (right).

was to compare the reversibility of lung function in asthmatic children after a dose of 200µg salbutamol that was inhaled either in a forward leaning body posture with the neck extended, or in a standard body posture. Forty-one asthmatic children were alternately included to inhale 200µg salbutamol with an Autohaler® in the standard or in the forward leaning body posture. The children in the forward leaning body posture group showed a significantly higher mean FEV_1 reversibility than the standard body posture group after inhalation of 200µg salbutamol. Additionally, mean MEF_{75} was significantly more reversible in the forward leaning body posture group versus the standard body posture group. This suggests that pulmonary effects of salbutamol can be improved by inhaling in a forward leaning body posture with the neck extended, possibly due to a higher pulmonary deposition of inhaled medication.

The pilot study as presented in chapter 4 was redesigned in **chapter 5** into a randomized cross over trial with children inhaling 200µg and 400µg salbutamol with a breath actuated inhaler in both the forward leaning posture and the standard posture. Twenty-two stable asthmatic children, aged 5-14 years, performed four spirometry measurements. The forward leaning posture during inhaling salbutamol did not result in a higher reversibility of the lung function variables compared to the standard posture. Reversibility of the FEV_1 was significantly higher after inhaling 400µg salbutamol compared to 200µg salbutamol in the standard posture. In conclusion, it seems that a forward leaning body posture during inhaling salbutamol with a breath actuated inhaler did not result in a higher reversibility in stable asthmatic children, in contrast to the results in other studies with other inhaler devices. Inhaling 400µg salbutamol compared to 200µg did result in a higher reversibility.

Previous studies have shown that a single dose of ICS offers acute, but moderate protection against EIB. The main objective of the study in **Chapter 6** was to investigate whether inhaling a single dose of ICS in a forward leaning posture improves the protection against EIB. Thirty-two asthmatic children with EIB, 5- 16 years, who did not use maintenance ICS, performed two ECT's on a jumping castle or a treadmill, preceded by the inhalation of a single dose BDP with a breath actuated

inhaler. They randomly inhaled once in the standard posture and once in the forward leaning posture with the neck extended. Spirometry was performed before inhalation of the single dose of 200µg BDP and again four hours later just prior to the ECT. Median fall in $FEV_{0.5}$ or FEV_1 at baseline without inhalation of BDP was 30.9% (IQR 21.8 ; 49.5%). Inhalation of BDP in both body postures provided similar protection against EIB (standard posture 16.7%; forward leaning posture 15.1%, p= 0.83). Inhaling ICS in a forward leaning posture significantly increased the time to maximum fall in FEV_1 after exercise compared to inhaling in the standard posture (respectively 2min 28sec ± 58sec vs. 1min 37sec ± 46sec; difference 51sec (95CI 15.0 ; 86.6sec); p=0.01). Inhaling in the forward leaning posture resulted in significant more bronchodilation compared to the standard posture in the four hours preceding the ECT (respectively 5% ± 9.4% vs. 1.1% ± 7.8%; difference 3.9% (95CI 0.2 ; 7.6%); p=0.04). In conclusion, inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in asthmatic children and the forward leaning posture resulted in a delay of EIB.

Previous studies also showed a protective effect of a single high dose of ICS against EIB in asthmatic children. **Chapter 7** describes a study that investigates the protective effect of a single low dose of 200µg ICS against EIB. Thirty-one children with EIB aged five to sixteen years who did not use maintenance ICS were included. They performed two ECT's within two weeks preceded by inhaling 200µg beclomethasone dipropionate (BDP) with a breath-actuated inhaler before the second ECT. The median fall in $FEV_{0.5}$ or FEV_1 after 200µg BDP was significantly reduced from 30.9% at baseline to 16.0% (p<0.001). Twenty children (64.5%) showed a good response to 200µg BDP (≥ 50% decrease in fall of $FEV_{0.5}$ or FEV_1), while eight children showed a moderate response (25-50%), and three children showed no response at all (< 25%). In conclusion, a low single dose ICS offers acute protection against EIB in the majority of asthmatic children who do not use ICS as maintenance therapy.

A recent study showed that in children with asthma, exercise not only triggered EIB but also induced post exercise inspiratory flow limitation. This phenomenon has also been demonstrated after bronchial challenges with histamine. The pathophysiology of inspiratory flow limitation is unclear. Salbutamol provides excellent protection against EIB, but the effect on inspiratory flow limitation is unknown. The bronchoprotective effect of salbutamol in EIB is largely attained by its stabilizing effect on mast cells. In **chapter 8** we investigated whether salbutamol protects against exercise induced inspiratory flow limitation in asthmatic children. Sixteen children 8-16 years old with documented exercise induced inspiratory flow limitation performed two ECT's. EIB was defined as a fall in forced expiratory volume in one second (FEV_1) ≥ 13% whereas inspiratory flow limitation was defined as a fall in mid inspiratory flow (MIF_{50}) ≥ 25%. Although salbutamol significantly reduced the mean exercise induced fall in MIF_{50} compared to placebo (17.6% versus 24.9%, p=0.004), half of the children showed no substantial response. Because we observed a large variability in the protective effect of salbutamol against exercise induced inspiratory flow limitation, it seems that inspiratory flow limitation is not entirely due to mast cell degranulation.

Bronchial hyperresponsiveness (BHR) is a key feature of childhood asthma lead-

ing to episodic respiratory symptoms. Long-term treatment with ICS reduces BHR does not benefit all children equally. At present there is a lack of diagnostic tools to assess this individual responsiveness to ICS that could aid clinical decision making and prevent inappropriate long term therapy. The severity of EIB is related to mannitol responsiveness. In **chapter 9** we hypothesized that the effect of a single dose of inhaled BDP on mannitol responsiveness could predict the effect of longer term therapy with BDP. Twelve children, 12-18 years, with mild to moderate asthma and symptoms of EIB who were deemed to start on BDP were recruited for this prospective study. The children performed a baseline mannitol challenge test and were started on a dose of twice daily 200µg BDP inhaled with a metered dose inhaler. Six hours after the first dose of 200µg BDP, a second mannitol challenge was performed and after four weeks of treatment a third mannitol challenge was performed 24 hours after the last BDP dose. Two children did not finish the study. Six children showed a reduction in mannitol responsiveness compared to baseline after both the single dose of BDP and after four weeks of treatment with BDP compared to baseline. The other four children did not show a reduction in mannitol responsiveness after a single dose of BDP and also not after four weeks of treatment with BDP compared to baseline. Intra class correlation (ICC) showed a strong correlation between the difference in mannitol responsiveness between baseline and after a single dose of BDP and the difference in mannitol responsiveness between baseline and after four weeks of BDP treatment (ICC 0.88). This relation could provide a useful tool to pursue a more individual approach regarding the start of ICS therapy.

Nederlandse samenvatting (Dutch summary)

OPTIMALISEREN VAN INHALATIETHERAPIE BIJ KINDEREN MET ASTMA

Astma is een veel voorkomende chronische ziekte die wordt gekarakteriseerd door ontsteking en episodische vernauwing van de luchtwegen. Inspanning is een belangrijke uitlokkende factor voor luchtwegvernauwing bij astmatische kinderen. Inspanningsastma is zeer specifiek voor astma en komt frequent voor (80-90%). Veel astmatische kinderen worden hierdoor gedwongen af te haken bij sport en spel en ervaren deze klacht dan ook als zeer beperkend. Klachten van inspanningsastma zijn bij jonge kinderen aspecifiek en worden niet altijd herkend door ouders, begeleiders en behandelaars, maar ook kinderen zelf waardoor een adequate behandeling soms niet wordt gegeven. Ook kunnen kinderen met astma zich aanpassen en inspanning vermijden teneinde klachten te ontlopen. Hierdoor kunnen verschillende aspecten van de ontwikkeling van kinderen en de kwaliteit van leven in het gedrang komen. Een inspanningsprovocatietest in de koude, droge lucht kan astma klachten door inspanning objectiveren en wordt gebruikt voor diagnostiek en evaluatie van astmatische klachten. Voor de behandeling van astma wordt vaak gebruikt gemaakt van inhalatiemedicatie. In dit proefschrift onderzoeken we verschillende aspecten van inhalatietherapie bij kinderen met astma met als doel deze te optimaliseren. Een introductie van de huidige stand van zaken is te vinden in **hoofdstuk 1**.

Veel kinderen met astma hebben hun klachten matig onder controle, wat veelal veroorzaakt wordt door therapie ontrouw. Uit de literatuur blijkt een gemiddelde therapietrouw van 60% onder astmatische kinderen. Bij jonge kinderen wordt de behandeling door de ouders gegeven en kunnen zij twijfels hebben over de diagnose en de behandeling van hun kind. Deze twijfels kunnen resulteren in therapieontrouw en enkel educatie lost dit probleem niet op. Andere factoren lijken mee te spelen welke belangrijke determinanten zijn voor therapietrouw. Hierbij kan een onderscheid gemaakt worden tussen onbewuste en bewuste therapieontrouw. Onbewuste therapieontrouw is gerelateerd aan praktische barrières in het dagelijks leven die therapietrouw in de weg staan, zoals beperkte structuur binnen de familie en problemen rondom het kind. Bewuste therapieontrouw heeft betrekking op ouders die hun eigen interpretatie geven aan de behandeling, gebaseerd op hun eigen ziekte perceptie en opvattingen over de medicatie. Ouders kunnen de controle over de klachten onder- of overschatten, omdat zij de klachten van hun kind niet goed kunnen duiden. Daardoor kunnen zij bijvoorbeeld het voorschrift van de dagelijkse medicatie naar hun eigen opvatting aanpassen.

Als ouders een inspanningsprovocatietest van hun kind bijwonen en zien dat hun kind door een korte inspanning astmatische klachten ontwikkelt, geobjectiveerd met behulp van een longfunctie meting, is het mogelijk dat zij meer doordrongen raken van de klachten van hun kind en de diagnose astma. Zij zien dat hun kind beperkt wordt in zijn/haar dagelijkse speelsituatie. Daarnaast worden ouders zich bewust van de lichamelijke symptomen van benauwdheid bij hun kind.

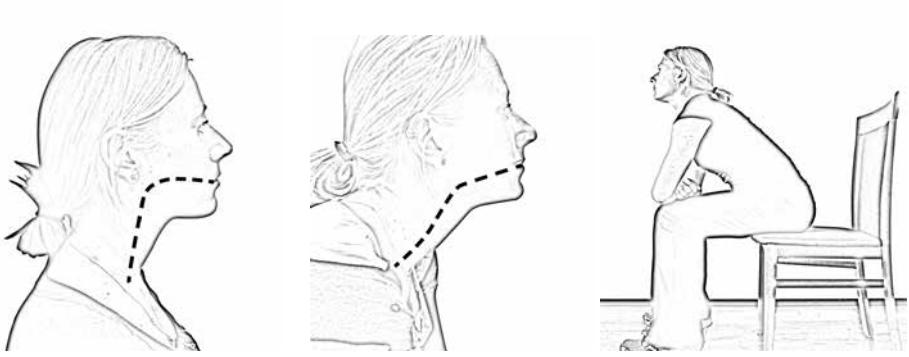
In **hoofdstuk 2** beschrijven wij een onderzoek waar we de effecten van het bespreken van het resultaat van een inspanningsprovocatietest op therapietrouw, ziekte perceptie en medicatie opvattingen van ouders analyseren. Onze hypothese was dat een kind waarbij inspanningsastma gediagnosticeerd wordt, het bewustzijn van ouders kan beïnvloeden en de therapietrouw kan verbeteren.

Negenenzeventig kinderen tussen vier en zeven jaar oud die bekend waren bij een kinderarts in verband met astmatische klachten in het Medisch Spectrum Twente in Enschede of Ziekenhuis Groep Twente in Hengelo of Almelo deden aan dit onderzoek mee. Zij voerden een inspanningsprovocatietest uit in koude, droge lucht op de overdekte ijsbaan Twente in Enschede. Voorafgaand aan de inspanningsprovocatietest hadden de kinderen zes weken lang een elektronische teller op hun medicatie inhalator gebruikt waarmee hun medicatie gebruik werd vastgelegd. Ook hadden hun ouders vragenlijsten ingevuld aangaande hun opvattingen over de ziekte en medicatie van hun kind. De uitslagen en de observaties van astma symptomen van de inspanningsprovocatietest werden direct na de test met ouders besproken, waarna opnieuw de vragenlijsten werden ingevuld. De teller op de inhalator werd tot 6 weken na de test gebruikt waarna de vragenlijsten voor de laatste maal werden ingevuld. De therapietrouw van deze groep kinderen voor de test was hoog, namelijk 83% en bleef in de periode na de test nagenoeg gelijk. Dit gold voor zowel de groep kinderen mét als zónder inspanningsastma. Zowel de kinderen met een hoge als een lage therapietrouw (respectievelijk ≥ 80% en <80%) lieten na de inspanningsprovocatietest geen significante verandering zien van therapietrouw. Uit de vragenlijsten bleek dat veel ouders al overtuigd waren van de noodzaak van de medicatie. Ook bleek dat bij het overgrote merendeel van de ouders (81%) de zorgen ten aanzien van het gebruik van de medicatie ondergeschikt waren aan de noodzaak. Na de inspanningsprovocatietest bleven deze scores nagenoeg gelijk (86%). Waarschijnlijk was er in deze groep kinderen met een hoge therapietrouw en een grote overtuiging tot de noodzaak van medicatiegebruik geen mogelijkheid voor verbetering door middel van het bespreken van de resultaten van een inspanningsprovocatietest. Meest waarschijnlijk was dit te danken aan het intensieve multidisciplinaire astma zorg programma voor deze groep kinderen, waar zowel de kinderarts als de astma verpleegkundige in participeren. We veronderstellen dat in de groep met lage therapietrouw onbewuste praktische barrières een belangrijke factor waren voor het niet verbeteren van de therapietrouw. Een intensief zorgprogramma lijkt een goed vangnet te bieden voor het voorkomen van bewuste therapieontrouw. In de toekomst zal de invloed van het bespreken van een inspanningsprovocatietestuitslag in een groep kinderen met bewuste therapie-ontrouw geanalyseerd moeten worden.

Inhalatie corticosteroïden (ICS) zijn vanwege hun ontstekingsremmende effect de standaard behandeling voor astma op alle leeftijden. Correct gebruik van de inhalatiemedicatie is een voorwaarde voor een succesvolle behandeling en fouten in het gebruik zijn geassocieerd met een verminderde astma controle. Veel astmatische kinderen inhaleren hun medicatie niet correct, zelfs na inhalatie instructie. In **hoofdstuk 3** evalueren we de inhalatietechniek zes weken na inhalatie instructie van jonge astmatische kinderen die regelmatig op controle komen bij een kinderarts. Ook onderzochten we de relatie tussen het opleidingsniveau van ouders en inhalatietechniek van hun kind. Eenennegentig astmatische kinderen van vier tot acht jaar oud werd gevraagd hun inhalatietechniek met een aerosol inhalator met voorzetkamer te demonstreren zoals zij in de thuissituatie ook gewend waren. Fouten in de inhalatietechniek werden vastgelegd met behulp van de checklist van het Nederlandse Longfonds. Direct na de demonstratie werden zowel de foute als de goede punten van de inhalatietechniek besproken met het

kind en de ouders. Zes weken later werd de inhalatietechniek opnieuw geëvalueerd waarbij bleek dat significant meer kinderen een perfecte inhalatietechniek demonstreerden (68.5% versus 36.3% aan het begin van de studie). Desondanks waren er significant meer kinderen die de essentiële fout maakten hun inhalator niet te schudden voor gebruik (16.9% versus 6.6% aan het begin van de studie). Schudden is noodzakelijk om dosis uniformiteit na te streven voor gebruik. De inhalatietechniek van het kind bleek niet geassocieerd te zijn met het opleidingsniveau van zijn/haar ouders. Concluderend was er sprake van verdubbeling van het aantal kinderen dat zes weken na inhalatie instructie een perfecte inhalatie techniek demonstreerden. Opvallend was dat er reeds na zes weken een significante stijging was van het aantal kinderen die de fout maakten hun medicatie niet te schudden voor gebruik. Bij een inhalatie instructie dient speciale aandacht gegeven te worden aan de noodzaak van het schudden van de medicatie en de reden hiervan.

Inhalatie medicatie slaat voor een aanzienlijk deel neer in de scherpe bocht van de luchtweg in de keelholte, waardoor de hoeveelheid die de longen bereikt sterk vermindert. Bij astmatische kinderen jonger dan 12 jaar slaat 50-60% van geïnhaleerd ICS met een ademgestuurde inhalator neer in de keel. In **hoofdstuk 4** beschrijven wij een pilot onderzoek waarbij het effect van inhaleren met salbutamol op de longfunctie wordt vergeleken in óf een voorover geleunde houding met het hoofd licht achterover, óf in de standaard lichaamshouding. In de voorover geleunde houding (figuur 1) wordt de bovenste luchtweg grotendeels gestrekt waardoor de scherpe bocht verdwijnt. Dit effect werd gemeten door middel van het blazen van longfunctie voor en na het inhaleren van salbutamol, een luchtwegverwijder. Eenenveertig astmatische kinderen die een geplande longfunctietest ondergingen inhaleerden 200µg salbutamol, ofwel rechtop (de standaard houding) ofwel in de voorover geleunde houding. De longfunctiemetingen werden allemaal in de standaard zittende houding uitgevoerd. Dit resulteerde in een grotere reversibiliteit van FEV_1 en MEF_{75} in de groep kinderen die voorovergeleund hadden geïnhaleerd ten opzichte van de groep kinderen die in de standaard houding had geïnhaleerd. FEV_1 en MEF_{75} zijn longfunctiewaarden die informatie geven over de kracht en snelheid van uitgeblazen lucht



Figuur 1: scherpe bocht in de luchtweg in de standaard inhalatiehouding versus gestrekte luchtweg in de voorovergeleunde lichaamshouding.

tijdens een krachtige uitademing. Deze waarden zijn vaak verminderd bij kinderen met astmatische klachten. Dit verschil in longfunctiewaarden suggereert dat het klinische effect van salbutamol geïnhaleerd met een adem gestuurde inhalator op de longen kan worden verbeterd door te inhaleren in een voorover geleunde houding met het hoofd licht achterover, waarschijnlijk ten gevolge van een grotere depositie van de medicatie in de longen.
De pilot studie beschreven in hoofdstuk 4 is verder uitgewerkt tot een gerandomiseerde cross-over trial beschreven in **hoofdstuk 5** waarbij de kinderen 200µg en 400µg salbutamol met een adem gestuurde inhalator in zowel de voorover geleunde houding als de standaard zittende houding geïnhaleerd hebben. Tweëentwintig stabiele astmatische kinderen tussen de vijf en veertien jaar oud voerden vier longfunctiemetingen uit. De voorover geleunde houding tijdens het inhaleren van salbutamol resulteerde niet in een grotere reversibiliteit van de longfunctiewaarden ten opzichte van de standaard lichaamshouding. Reversibiliteit van de FEV_1 was wel significant groter bij het inhaleren van 400µg salbutamol ten opzichte van de 200µg salbutamol in de standaard lichaamshouding (4.5% ± 7.5% vs. 9.4% ± 9.5%, verschil 4.9%). Concluderend lijkt een voorover geleunde lichaamshouding tijdens het inhaleren van salbutamol met een adem gestuurde inhalator niet tot grotere reversibiliteit te leiden bij stabiele astmatische kinderen in tegenstelling tot wat gezien wordt bij andere methoden van inhaleren. Inhaleren van 400µg salbutamol ten opzichte van 200µg leidde wel tot een grotere reversibiliteit.
Uit voorgaand onderzoek is gebleken dat een hoge enkele dosis ICS (1000-1600µg) een acute bescherming geeft tegen inspanningsastma. Doel van de studie beschreven in **hoofdstuk 6** was om te analyseren of een veel lagere dosis van 200µg ICS in de voorover geleunde houding ook beschermt tegen inspanningsastma. Tweeëndertig astmatische kinderen tussen de vijf en zestien jaar oud met inspanningsastma, die geen corticosteroïden als onderhoudsmedicatie gebruikten, voerden twee inspanningsprovocatietesten uit op het springkussen of de loopband in de koude, droge lucht op de overdekte ijsbaan, waarbij zij vier uur van tevoren een enkele dosis 200µg ICS kregen met behulp van een adem gestuurde inhalator. Zij inhaleerden gerandomiseerd eenmaal in de standaard zittende houding en eenmaal in de voorover geleunde houding. Zowel inhaleren van 200µg ICS in de voorover geleunde houding als de standaard zittende houding beschermden significant tegen inspanningsastma (daling FEV_1 zonder ICS 30.9%; daling FEV_1 met ICS in standaard zittende houding 16.7%; daling FEV_1 met ICS in voorover geleunde houding 15.1%). De bescherming tussen de twee houdingen verschilde niet significant. Het inhaleren in de voorover geleunde houding leidde wel tot een vertraging van het optreden van de maximale daling van de FEV_1 vergeleken met de standaard zittende houding (respectievelijk 2min 28sec ± 58sec vs. 1min 37sec ± 46sec). Inhaleren in de voorovergeleunde houding resulteerde in significant meer luchtwegverwijding ten opzichte van inhaleren in de standaard lichaamshouding in de vier uur periode voor de test (respectievelijk 5% ± 9.4% vs. 1.1% ± 7.8%). Concluderend leidde inhaleren van 200µg ICS met een adem gestuurde inhalator in een voorover geleunde houding niet tot meer bescherming tegen inspanningsastma maar wel tot een vertraging van het optreden van inspanningsastma vergeleken met inhaleren van ICS in de standaard zittende houding.

ICS worden primair als onderhoudsmedicatie gebruikt. Voorgaande studies laten zien dat een enkele hoge dosis ook een beschermend effect heeft op de luchtwegvernauwing door bijvoorbeeld inspanning. **Hoofdstuk 7** beschrijft de analyse van het beschermende effect op inspanningsastma van een enkele lage dosis ICS van 200µg. Eenendertig kinderen met inspanningsastma tussen de vijf en zestien jaar oud, die geen corticosteroïden als onderhoudsmedicatie gebruikten werden geïncludeerd. Zij voerden twee inspanningsprovocatietesten uit binnen twee weken waarbij zij vier uur voorafgaand aan de tweede inspanningsprovocatietest 200µg ICS met een adem gestuurde inhalator inhaleerden. De gemiddelde daling van de FEV_1 nam significant af van 30.9% bij de eerste test, naar 16.0% na de tweede test na inhaleren van ICS. Twintig kinderen (64.5%) lieten een goede reactie zien op inhaleren van ICS (≥50% verbetering), acht kinderen lieten een gemiddelde reactie zien (25-50% verbetering) en twee kinderen lieten geheel geen reactie zien. Concluderend biedt een enkele lage dosis ICS acute bescherming tegen inspanningsastma bij de meerderheid de astmatische kinderen die geen onderhoud ICS gebruiken.

Een recente studie heeft aangetoond dat inspanning bij astmatische kinderen niet alleen kan leiden tot de bekende expiratoire luchtwegvernauwing, maar ook tot inspiratoire flow limitatie. De pathofysiologie van inspiratoire flow limitatie is nog onduidelijk. Salbutamol geeft een goede bescherming tegen expiratoire luchtwegvernauwing (gemeten middels de FEV_1), door het remmende effect op degranulatie van mestcellen waarbij histamine vrij komt. Het effect van salbutamol op inspiratoire flow limitatie is echter onbekend. Doel van het dubbel-blinde, placebo gecontroleerde, prospectieve gerandomiseerde onderzoek beschreven in **hoofdstuk 8** was het analyseren van een mogelijk beschermend effect van salbutamol tegen inspiratoire flow limitatie bij astmatische kinderen. Zestien kinderen met inspiratoire flow limitatie tussen de acht en zestien jaar inhaleerden gerandomiseerd éénmaal 200µg salbutamol en éénmaal een placebo voorafgaand aan een inspanningsprovocatietest in de koude, droge lucht op de overdekte ijsbaan. Expiratoire luchtwegvernauwing werd gedefinieerd als een daling van de FEV_1 van ≥13%, en inspiratoire flow limitatie werd gedefinieerd als een daling van de mean inspiratoire flow van ≥ 25% bij 50% van de vitale capaciteit (MIF_{50}). Salbutamol verminderde de gemiddelde daling van de MIF_{50} ten gevolge van inspanning significant vergeleken met placebo (17.6% vs. 24.9%), maar de helft van de kinderen liet geen significante reactie zien op het gebruik van salbutamol. Concluderend was er sprake van een grote variabiliteit in het beschermende effect van salbutamol tegen inspiratoire flow limitatie ten gevolge van inspanning wat suggereert dat de inspiratoire flow limitatie niet volledig is toe te schrijven aan degranulatie van de mestcellen. Voor de klinische praktijk betekent dit dat aanhoudende inspanningsgebonden luchtwegklachten bij kinderen met astma ondanks profylaxe met salbutamol kunnen worden veroorzaakt door inspannings geinduceerde inspiratoire flow limitatie.

Inspanningsastma is een belangrijk symptoom van astma op de kinderleeftijd. Hoewel ICS inspanningsastma kunnen verminderen, varieert dit effect per patiënt. Op dit moment is er een tekort aan diagnostische mogelijkheden om de grootte van het individuele effect op ICS behandeling te voorspellen. De ernst van inspanningsastma correspondeert met luchtweg hyperreactiviteit die aangetoond kan worden bij een mannitol test en kan gebruikt worden om inspanningsastma te

diagnosticeren en te vervolgen. Bepalen van de individuele luchtweg hyperreactiviteit gevoeligheid voor een eenmalige dosis ICS met behulp van mannitol zou een indicatie kunnen geven van het effect van ICS op de langere termijn. Doel van het onderzoek beschreven in **hoofdstuk 9** was om de relatie te onderzoeken tussen het effect van een enkele dosis ICS en vier weken behandeling met ICS op de luchtweg hyperreactiviteit gemeten met een mannitol test. Twaalf kinderen tussen de 12 en 18 jaar oud met mild tot matig astma en symptomen van inspanningsastma die gingen starten met ICS onderhoudsbehandeling werden geïncludeerd in deze prospectieve studie. De kinderen voerden een baseline mannitol test uit en binnen een week een tweede mannitol test voorafgegaan door een enkele dosis van 200µg ICS. Na vier weken onderhoudsbehandeling met tweemaal daags ICS voerden zij een derde mannitol test uit. Twee kinderen hebben de studie niet afgemaakt. Zes van de tien overige kinderen lieten zowel een vermindering van de luchtweg hyperreactiviteit op de mannitol test zien na een enkele dosis ICS als na vier weken behandeling met ICS. De overige vier kinderen die geen verbetering lieten zien na een enkele dosis ICS, deden dit ook niet na de vier weken behandeling met ICS. De verandering van luchtweg hyperreactiviteit na een enkele dosis ICS en na vier weken behandeling met ICS bleek dus sterk gecorreleerd (intra class correlation 0.88). Dit betekent dat de uitslag van de mannitol test na 1 gift ICS sterk samenhangt met de uitslag van de mannitol test na 4 weken ICS gebruik. Dit kan in de klinische praktijk gebruikt worden om met een mannitol test na 1 gift ICS het effect te kunnen voorspellen van langdurig ICS gebruik op astmatische klachten. Deze relatie geeft mogelijkheden om te komen tot een meer individuele benadering bij de keuze van medicatie voor kinderen met astma.
Gezien het kleine aantal kinderen dat aan deze studie meegedaan heeft, gaat deze studie in de toekomst vervolgd worden met uitbreiding van het aantal deelnemers om op deze manier de betrouwbaarheid te vergroten.

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DANKWOORD

"Everyone needs help: It takes a village to do research"

Het dankwoord van mijn proefschrift…Wat zijn er veel mensen te noemen die hebben bijgedragen aan het voltooien van mijn werk.

Allereerst Boony, zonder jou was dit proefschrift niet tot stand gekomen. Jij hebt mij met je kennis, inzichten, positieve stemming, optimisme en oplossingsgerichtheid zoveel geleerd! We zijn een goed onderzoeksteam: jij het brein en de creatieve geest, ik droeg zorg voor de planning, organisatie en de structuur. Jouw chaos was soms een beetje lastig, soms erg lachwekkend: je eigen handschrift niet meer kunnen lezen (Ik: "Nee kijk Boony, hier staat een sterretje, die verwijst naar nummer 1, dan schrijf je door op blz. 7 en volgens mij bedoel je dat het deel met de 6 sterretjes bij de abstract hoort". Jij: "Ja inderdaad! Dat was de bedoeling. Nou, als je dát kan volgen ben je rijp voor je promotie"). Of die keer dat je een deel van mijn artikel op papier kwijt was, welke in stukjes gescheurd in een sinterklaas-surprise grabbelton was beland: "Wacht even Reina, ik plak hem nu weer aan elkaar!" Naast onze wetenschappelijke samenwerking hebben wij ook een sportieve connectie. Gesprekken over inspanningsastma, inhalatiehoudingen, longfuncties, medicatie en springkussens werden afgewisseld met de marathon van Rotterdam, hardloopschema's, mountainbike weetjes en sportvoeding. Wij begrepen elkaar en jij liet mij vrij in mijn planning en organisatie om werk en sport optimaal te kunnen combineren. Daar ben ik je dankbaar voor en ik zie dat als een bijzondere vorm van vertrouwen. Verder denk ik met een lach terug aan onze hardlooptraining langs de kust in San Diego waarna we bíjna in een Amerikaanse pool party terecht kwamen, aan ons muzikale verblijf in het Hard Rock Hotel waarbij we tot diep in de nacht gitaar hebben gespeeld, de middag dat jij een halve Apple winkel leeg gekocht hebt aan de hand van een boodschappenlijstje samengesteld door al jouw gezinsleden die achtergebleven waren in Nederland, en aan die avond in een strand-restaurant in Barcelona waarbij jij niet te stoppen was in het tappen van (net iets te schuine) moppen.

Job, mijn promotor, mijn adviseur, mijn klankbord en mijn rots in de branding. Job, jij was er altijd, van 's ochtends vroeg tot 's avonds laat, e-mails beantwoordend op zaterdag- of zondagavond tijdens de reclame die een film onderbrak. Jij hebt voor alle statistische uitdagingen een oplossing, maar bent bovenal op wonderbaarlijk wijze in staat alle cijfers, grafieken en formules met praktische voorbeelden tot leven te laten komen. Onder het genot van een kopje kistje-van-de-keizer thee tijdens onze besprekingen op jouw kamer begon zelfs een statistische nul, die ik was toen ik aan dit avontuur begon, statistiek te snappen. Ook met jou deel ik de passie voor sport; jij meent niet voor hardlopen in de wieg gelegd te zijn, wel voor wielrennen, bij mij is dit precies andersom. Ik wilde mij echter niet laten kennen en ben eens met jou op de wielrenner van Enschede naar jouw huis in Deventer gefietst. Jouw vraag of we op de Holterberg de korte of de lange route zouden nemen leidde bij mij, geheel tegen mijn normale instelling in, tot een timide: "doe de korte weg maar, dan doen we de volgende keer de lange". Gelukkig stond er

bij thuiskomst in Deventer een heerlijke avondmaaltijd klaar, waarna ik de ontberingen van onderweg zowaar alweer vergeten was. Daarnaast heb ik warme herinneringen aan samen échte tortilla's eten aan de Amerikaans-Mexicaanse grens, winkelen in San Diego en een gokje wagen in Las Vegas☺.

Leden van mijn promotiecommissie, hartelijk dank voor het bestuderen en evalueren van mijn proefschrift.

Werken op de ijsbaan is leuk, maar vaak wel koud. Warme kleding helpt, maar gezelligheid nog meer. Tijdens mijn eerste winter op de ijsbaan kreeg ik regelmatig hulp van Laura die vrijwillig wat meer ervaring in de onderzoekswereld wilde op doen. Samen raakten we wegwijs in de praktische kanten van het uitvoeren van inspanningstesten. In het tweede jaar kreeg ik gezelschap van Beike en Mariet, welke beiden hun wetenschapsstage op onze afdeling uitvoerden. Onder het genot van een kop chocomelk zijn de humoristische, eerlijke en recht-toe-recht-aan uitspraken van de kinderen nog leuker als je er sámen om kan lachen. We ervoeren dat onderzoek aanleiding kan geven tot veelzijdige activiteiten zoals het knutselen van een waardige grabbelton en interviews geven voor de krant tot het zoeken van de meest geschikte snowboots en het volgen van het sinterklaasjournaal om de wachttijd met de kleuters vol te kletsen. Mariet en Beike, jullie hebben mij met jullie assertieve instelling en enthousiasme op vele vlakken bijgestaan!

Sophie, bedankt voor jouw inzet aangaande het reversibiliteitsonderzoek. Vol enthousiasme stortte jij je in de wereld van de astma op kinderleeftijd en je toonde je assertief op vele vlakken. Altijd vrolijk en positief, ook als je het even niet zag zitten. Het klikte met de kinderen, zowel met de kleuters als de schoolkinderen, de pubers en met mij. Ons onderzoek verliep eigenlijk optimaal en jij verbaasde jezelf door met een beetje hulp zowaar een weg te vinden door het bos der statistieke formules.

Tante Machteld, bedankt voor de prachtige cover en al je werk aan de opmaak van dit proefschrift! Jij hebt ervoor gezorgd dat alles op tijd af was en was onvermoeibaar aangaande het aanpassen van alle details.

Marjolein, bedankt voor je enthousiaste hulp bij de statistiek en het schrijven van onze artikelen.

Sandy, thank you very much for your contribution to my thesis. Your experience, energy and enthusiasm are admirable.

Ted, jij bent voor mij als ervaren onderzoeker een bron van tips, aanwijzingen en kennis geweest. Je was er ook om mij door de uitdaging van het schrijven van mijn eerste artikel te leiden.

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Frans, bedankt voor het overdragen van je brede kennis op het gebied van longfunctie metingen. Je bent bijzonder geschikt als docent, na een bezoek aan jou voelde ik me veel zekerder van mijn zaak.

Alle medewerkers van de longfunctieafdeling van het MST; jullie ontvingen mij met open armen en dankzij jullie behulpzaamheid en betrokkenheid kijk ik terug op een heel plezierige periode op de longfunctie afdeling.

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Alle collega's van de kinderafdeling van het MST, in het bijzonder Anne (Schoot) wil ik bedanken voor de steun, interesse en het het meedenken. Daarnaast ook dank voor de collega's in het ZGT Hengelo en Almelo die open stonden voor deelname aan het IMPACT onderzoek.

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Lieve VWO vrienden, wat hebben wij een bijzondere hechte vriendschap en wat geniet ik ervan dat we elkaar blijven zien. De jaarlijkse weekendjes weg zijn een hoogtepunt, maar ook simpelweg bijkletsen met een kopje thee en gedeelde herinneringen ophalen ervaar ik als heel waardevol. Annemarie en Manon, 26 jaar nadat we elkaar leerden kennen in groep 0/1 bij juffrouw José zijn we nu nog steeds hecht bevriend, en wat ben ik daar blij mee!

Anne (Akkerman), kinderarts in opleiding en ex-collega uit het MST, je bent een belangrijke trouwe vriendin voor me gebleven, ook al woon je al een tijd niet meer in het oosten.

Hardloopvrienden, met name ons estafette-team Aeolus en (mijn ex-trainer) Thijs, ook al ben ik de afgelopen 1,5-2 jaar minder in beeld geweest bij de grote wedstrijden en heb ik minder deel kunnen nemen aan sociale activiteiten ten gevolge van mijn opleiding in Leiden, jullie blijven een stabiele betrouwbare groep mensen bij wie ik veel plezier en ontspanning ervaar.

Mijn lieve paranimfen, Heleen en Anne (de Grauw), bedankt dat jullie deze dag aan mijn zijde willen staan. Ik ken jullie sinds mijn studententijd in Nijmegen. Anne, medestudent, al snel een goede vriendin, had net als ik een passie voor kindergeneeskunde. Op jouw advies heb ik ruim 2 jaar geleden mijn sollicitatiebrief naar het LUMC in Leiden gestuurd, waar jij al in opleiding was tot kinderarts, en inmiddels weten we allemaal wat dat me heeft opgeleverd. Ik zal nooit vergeten dat ik dit mede aan jou te danken heb. Heleen, wij werden in Nijmegen als door een soort toeval hardloopvriendinnen, jij bleek al arts te zijn en hebt heel wat ervaringen, tips en trucs met mij gedeeld wat betreft coschappen, het ziekenhuisleven en een baan zoeken. Bovenal zijn jullie twee vriendinnen die altijd voor mij klaar staan en dat is een waardevol gevoel.

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En uiteindelijk het belangrijkste: de kinderen. Zonder de kinderen geen metingen, en dus ook geen proefschrift. De kinderen hebben mij bij de les gehouden, zij zorgden voor afwisseling, brachten emotie, een lach, verbazing. Elk kind is uniek. Een kadootje, tekening, knutselwerk of knuffel van een kind geeft je dag kleur. De kinderen bevestigden mijn overtuiging: kinderen geven mij plezier en inzicht, laten mij relativeren, kunnen mij confronteren en ik kan veel van ze leren. Dat is waarom werken met kinderen mij zo intrigeert.

Lieve mam, zus en familie: jullie waren er met een luisterend oor, duwtje in de rug, praktische tips, of gewoon de oplossing die altijd helpt: chocolade. Lieve schoonfamilie, bedankt voor de plek in jullie warme, gastvrije gezin. Anne (Veltman) bedankt voor je steun tijdens de eerste periode van mijn promotie, met praktische oplossingen, meedenken en aanpakken.

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Allerliefste Sander, kern van mijn leven, mijn grote liefde, altijd mijn zonneschijn, zelfs als het even regent. Bedankt dat je voor, naast en achter me staat. Wat zijn alle hordes die we hebben overwonnen het waard geweest, ons leven samen is prachtig!

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Ik draag dit proefschrift op aan jou 

Reina

List of publications

The effect of body posture during medication inhalation on exercise induced bronchoconstriction in asthmatic children
Resp Med, 2015, 1257-61
R. Visser, M. Wind, B. J. de Graaf, F. H.C. de Jongh, J. van der Palen, B. J. Thio

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Curriculum Vitae

Reina Visser was born on December 2, 1985 in Enschede. She grew up in the small village of Neede, near Enschede, where she went to primary school and also attended the first years of high school. From her 14th year she had a clear vision of what profession she wanted to pursue later: pediatrician.
In 2004 she graduated from the Assink Lyceum in Haaksbergen and started studying medicine at the Radboud University in Nijmegen to start realising her dream.

During her study she initiated and participated in various activities and projects to expand her pediatric knowledge and experience, for example the Teddy Bear Hospital, research at the department of pediatric surgery and a major research project in the Department of Neonatology.

After her medical graduation in 2010, she started working as a resident at the pediatric ward of the Medisch Spectrum Twente in Enschede. Within a year she started combining her clinical work with medical research in the field of exercise induced asthma in childhood under the guidance of dr. B.J. Thio, which resulted in this thesis.

In 2014 Reina started her pediatric training at the University Medical Center in Leiden supervised by dr. W.J.W. Kollen. During the first two years of this training she completed her thesis.

Reina lives together with Sander, Jade and Ruby in Enschede. Besides her passion pediatrics, she is a top athlete, running long distances up to the marathon, she loves to ride her motor bike and likes movies, music, photography and hiking.