Exercise induced bronchoconstriction in childhood asthma
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Chapter 5

Measuring breakthrough exercise induced bronchoconstriction in young asthmatic children using a jumping castle

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ABSTRACT

Background
Asthma in early childhood is difficult to recognise. Exercise induced bronchoconstriction (EIB) is highly specific for asthma, but not widely studied in children <8 years. In asthmatic children >8 years, EIB can occur during exercise, ie, breakthrough EIB. EIB has been documented in children <8 years, but breakthrough EIB has not been studied in this age group.

Objective
This study investigates breakthrough EIB in young asthmatic children and examines the feasibility of using a jumping castle to identify EIB.

Methods
In this cross-sectional, observational study, children aged 5-7 years with asthmatic symptoms underwent a novel exercise challenge test. Children jumped for 6 minutes on a jumping castle in cold, dry air, achieving a target heart rate of >80% of predicted maximum. FEV\textsubscript{0.5} was measured before, during and after exercise (at 0,1,2,3,5,7,10 and 15 minutes). Breakthrough EIB and EIB were both defined as a fall in FEV\textsubscript{0.5} ≥13% from the pre-exercise value.

Results
87 Exercise challenge tests were performed in 82 children, with a success rate of 93.1%. 43 children showed EIB with the median maximum fall being 2 minutes after exercise. In the children with EIB, 36% had breakthrough EIB, occurring between 2 and 6 minutes of exercise. Breakthrough EIB was accompanied by a significantly greater maximum fall in FEV\textsubscript{0.5} after exercise.

Conclusion
EIB can occur rapidly during exercise in young asthmatic children and this breakthrough EIB is indicative for severe EIB. An exercise challenge test using a jumping castle is suitable for diagnosing EIB in young children.
EIB in 5-7 year old children

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways, affecting approximately 300 million people worldwide.\textsuperscript{1,2} Diagnosing asthma at a young age enables therapeutic intervention at an early stage of disease, preventing long-term remodelling of the airways and improving the prognosis of asthma.\textsuperscript{3} However, asthma in early childhood is difficult to recognise, for clinicians, parents and children.\textsuperscript{2,4} Children are often treated for asthma based on clinical and historical features, which prove not to be specific measures for diagnosing asthma.\textsuperscript{2,4}

Exercise induced bronchoconstriction (EIB) has been defined as a transient narrowing of the airways that follows vigorous exercise.\textsuperscript{5} The airway narrowing is measured indirectly as a fall in the forced expiratory volume in 1 second (FEV\textsubscript{1}) or the forced expiratory volume in 0.5 second (FEV\textsubscript{0.5}). EIB is highly specific for asthma in children and exercise is an indirect provocation test that can be used to diagnose and evaluate asthma.\textsuperscript{4,8} Exercise challenge tests (ECTs) have been studied extensively and are standardised for children older than 8 years.\textsuperscript{9} However, performing a safe, effective, and sustainable ECT in younger children is a challenge in itself.

In many asthmatic children over 8 years of age, EIB occurs during exercise and is sustained after exercise; this is known as breakthrough EIB.\textsuperscript{10} Also, there seems to be an important relation between age and the pattern of EIB; the younger the child, the shorter the time to maximal bronchoconstriction and the quicker the recovery from EIB.\textsuperscript{11,12} Few studies have documented EIB in children less than 8 years of age, and decreases in FEV\textsubscript{0.5} during exercise (breakthrough EIB) have not been investigated in this age group.\textsuperscript{7,11,13}

We describe a novel ECT to examine EIB and the frequency of breakthrough EIB in young asthmatic children using a jumping castle, an inflatable platform on which children can safely jump.

METHODS

Subjects

This study was of a cross-sectional, observational design and conducted between November 2011 and March 2012. We recruited children born between January 2004 and January 2007, with a history of asthmatic symptoms, from the outpatient clinic of the pediatric department of Medisch Spectrum Twente, Enschede, the Netherlands. Children underwent an extensive evaluation of their asthma, including a disease history, a questionnaire (Childhood Asthma Control Test; C-ACT)\textsuperscript{14} and the novel ECT. No short- and long-acting bronchodilators were permitted 8 and 24 hours, respectively, before testing. Leukotriene receptor antagonists were withheld at least 24 hours before
testing. Other exclusion criteria were the presence of pulmonary or cardiac co-morbidity and clinically unstable asthma (ie, hospital admission or use of systemic corticosteroids 4 weeks before testing). The study was approved by the Medical Ethics Committee Twente, Enschede, the Netherlands, and registered under number NTR3038 in the Dutch Trial Register (www.trialregister.nl). All parents received written patient information and signed an informed consent form before study entry.

**Spirometry**

Pulmonary function (FEV$_{0.5}$ and FEV$_{1}$) was measured before (baseline), during and after exercise using a standardised protocol according to international guidelines$^{15}$. We used a Microloop MK8 Spirometer with impeller (ML3535$^{®}$), with Spida5$^{®}$ software to measure flow volume curves. Calibration of the spirometer was frequently checked.

Baseline spirometry comprised performing expiratory flow volume curves in duplicate. During and after exercise, single flow volume curves were recorded. A skilled investigator (JvL), trained in pediatric spirometry, instructed the children to perform a maximal expiratory effort from inspiratory vital capacity to residual volume. Visual incentives were used to optimise spirometry. Children were seated, and for reasons of comfort, they did not wear a nose clip.

The best values for FEV$_{0.5}$ and only technically correct flow volume curves were used for analysis, as recommended by Vilozni et al.$^{7}$. An exercise induced decrease in FEV$_{0.5}$ of 13% or greater from baseline was considered diagnostic of both EIB and breakthrough EIB$^{7,16}$. Reference values for FEV$_{0.5}$ and FEV$_{1}$ were calculated according to the method of Koopman et al., because these values have been updated recently and resemble our study population with regard to age and race$^{17}$.

**Exercise challenge test**

The ECT consisted of jumping on a jumping castle. The jumping castle was regularly vacuumed and had an uncovered jumping area. Cold, dry air with a temperature of 9.5-10.0 °C and humidity of 57-59% (5.5-6.0 mg H$_2$O/l) was obtained while testing in the local ice skating rink, IJsbaan Twente, Enschede, the Netherlands. Resurfacing of the ice was done with electrically driven resurfacing machines. During exercise, heart rate was continuously monitored by use of radio telemetry (Sigma Sport PC3). The target was to complete 6 minutes of exercise and achieve at least 80% of the predicted maximum heart rate (0.8x [220-age]$^{6}$), for a minimum of 4 minutes$^{7}$. After 2 and 4 minutes of jumping, exercise was briefly interrupted (maximum 20 seconds) and children performed a single flow volume curve, after which exercise was immediately resumed. After exercise, single flow volume curves were performed at 0,1,2,3,5,7,10 and 15 minutes. In case of a technically unacceptable flow volume curve the attempt was repeated once. We observed whether the children had bronchoconstriction that was symptomatic, with
signs of shortness of breath (dyspnea), coughing, wheezing, retractions and the use of accessory muscles of breathing.

If bronchoconstriction persisted 15 minutes after exercise (defined as a decrease in $\text{FEV}_{0.5}$ of $>5\%$ from baseline value) or at children’s request, a short-acting $\beta_2$-agonist (100 $\mu$g of salbutamol administered through a spacer) was administered, and a flow volume curve was repeated 5 minutes afterwards to confirm recovery.

**Questionnaire**

Children and parents filled out the C-ACT, a validated questionnaire assessing asthma control in children aged 4 to 11 years\textsuperscript{14}. It consists of 7 questions; 4 child-completed items with a 4-point visual response scale and 3 parent-completed items with a 6-point response scale\textsuperscript{14}. The C-ACT score is the sum of all scores, ranging from 0 (poorest asthma control) to 27 (optimal asthma control). A score of less than 20 points indicates inadequately controlled asthma\textsuperscript{14,18}.

**Statistical analysis**

Results were expressed as means ± standard deviations (SDs) for normally distributed data, as medians (minimums;maximums) for nonnormally distributed data, or as numbers with corresponding percentages if nominal or ordinal. Continuous variables were tested for normality with a Shapiro-Wilk or Kolmogorov-Smirnov test, as appropriate. Differences in characteristics between groups were determined by using the Chi-Square test, Fisher exact test, Mann-Witney U test, and independent samples t-test (if normally distributed). Correlations were calculated using Spearman correlation. A 2-sided value of less than 0.05 was considered statistically significant. All analyses were performed with the Statistical Package for the Social Sciences (SPSS\textsuperscript{*}) for Windows\textsuperscript{*} version 15 (IBM, Chicago, IL, USA).

**RESULTS**

**Study population**

Eighty-seven ECTs were performed in 82 children (45 male) with a mean age of 6.2 ± 0.8 years. 5 Children performed the ECT twice at a parent’s request because of a medication regimen change or an unexpected outcome.

**Exercise challenge test**

In 6 (6.9\%) children the ECT could not be performed reliably; 5 children were unable to produce technically acceptable spirometric results (both male and female, mean age 5.8 years), and 1 child did not reach the target heart rate during exercise (73\% of maximum).
In all other children the ECT was reliable. Flow volume curves were technically acceptable for analysis of FEV\textsubscript{0.5} before, during and after exercise. In 64 (79%) of 81 children, analysis of FEV\textsubscript{1} could also have been used to diagnose or exclude EIB. However, FEV\textsubscript{1} in young children is likely to be less reliable than FEV\textsubscript{0.5} because most young children are unable to perform the required full forced expiration during a total second, especially during exercise. For example, for 56 (69%) of the children, the baseline Tiffeneau index (FEV\textsubscript{1}/forced vital capacity x 100) was 90% or greater, demonstrating that FEV\textsubscript{1} almost equaled forced vital capacity.

The type of exercise (ie, jumping on a jumping castle) was effective in increasing heart rate, and within 1 minute, 97% of the children had a heart rate of greater than 80% of maximum value, which was easily sustained throughout the ECT. None of the children hesitated to jump, and all children jumped the entire 6 minutes, except for 3 children with severe breakthrough EIB in whom exercise was terminated after 4 or 5 minutes.

**Exercise induced bronchoconstriction**

Forty-three of 81 children had EIB using this novel ECT. Characteristics of children with and without EIB are shown in table 1. Children with EIB had significantly more complaints of exercise induced dyspnea (71.4% vs. 40.5%, p=0.01) and significantly more signs of EIB during and after exercise. As shown in table 1, the presence of coughing in combination with one other asthma symptom during exercise is characteristic for EIB. However, coughing alone also occurs in children without EIB. Baseline FEV\textsubscript{0.5} was significantly less in children with EIB compared with that seen in children without EIB (80.5% ± 15.6% vs 88.0% ± 14.6% predicted, p=0.03). There was no significant difference in mean C-ACT scores between children with or without EIB and the C-ACT score was not related to the percentage exercise induced decrease in FEV\textsubscript{0.5} (r=-0.04, p=0.72) (figure 1). Twenty-seven of the children with a C-ACT score of 20 or greater and in the range consistent with asthma control had EIB, and in the majority (81%) this was a greater than 20% decrease in FEV\textsubscript{0.5}.

The pattern of EIB in young children is shown in figure 2. Mean FEV\textsubscript{0.5} decreased during exercise and kept decreasing after exercise, with the lowest value being recorded at 2 minutes. This was followed by spontaneous recovery of FEV\textsubscript{0.5} over approximately 15 minutes. In 57% of the children with EIB and 53% of the children without EIB (p=0.69), FEV\textsubscript{0.5} initially increased during exercise. There is no significant difference in the median increase in FEV\textsubscript{0.5} during exercise between children with or without EIB, nor did we find a relation between baseline FEV\textsubscript{0.5} (percent predicted) and the percentage increase in FEV\textsubscript{0.5} during exercise (r=-0.13, p=0.24).
In 36% of the children with EIB, bronchoconstriction (ie, decrease in FEV$_{0.5}$ ≥13% from baseline value) occurred during the 6-minute exercise test. Children with this breakthrough EIB were compared to children with non-breakthrough EIB in table 2. Children with breakthrough EIB had a significantly lower baseline pulmonary function, a signifi-
cantly greater maximum exercise induced decrease in FEV\textsubscript{0.5} and a slower recovery from EIB compared with children with non-breakthrough EIB. The C-ACT score was marginally lower in children with breakthrough EIB and they tended to be younger than children with non-breakthrough EIB.

The pattern of EIB in children with breakthrough and non-breakthrough EIB is shown in figure 3. In the breakthrough EIB group mean FEV\textsubscript{0.5} rapidly decreased during exercise, in some children even within 2 minutes. After exercise, FEV\textsubscript{0.5} progressively decreased, with a maximum decrease at 2 minutes, after which spontaneous recovery of FEV\textsubscript{0.5} occurred. In non-breakthrough EIB a small increase in mean FEV\textsubscript{0.5} in the first 2 minutes of exercise was followed by a slow decrease in FEV\textsubscript{0.5} during the last few minutes of exercise and a more rapid decrease after exercise. At all measured points mean FEV\textsubscript{0.5} (as percentage of predicted) was significantly lower in the children with breakthrough EIB (figure 3B).

Figure 1. Relation between C-ACT score and percentage exercise induced decrease in FEV\textsubscript{0.5} (N = 81). C-ACT, childhood asthma control test; FEV\textsubscript{0.5}, forced expiratory volume in 0.5 second. Dotted lines represent cutoff value for EIB (ie, 13% decrease in FEV\textsubscript{0.5}) and cutoff value for asthma control (score of <20 is defined as inadequately controlled asthma).
Table 2. Characteristics of children with breakthrough or non-breakthrough EIB.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Breakthrough EIB (N=15)</th>
<th>Non-breakthrough EIB (N=27)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>5.9 ± 0.7</td>
<td>6.4 ± 0.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Male</td>
<td>7 (46.7)</td>
<td>15 (55.6)</td>
<td>0.58</td>
</tr>
<tr>
<td>Exercise induced symptoms</td>
<td>9 (60)</td>
<td>20 (76.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Allergy*</td>
<td>9 (60)</td>
<td>**15 (68.2)</td>
<td>0.61</td>
</tr>
<tr>
<td>Medication use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SABA</td>
<td>14 (93.3)</td>
<td>21 (77.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>LABA</td>
<td>1 (6.7)</td>
<td>0 (0.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>ICS</td>
<td>11 (73.3)</td>
<td>16 (59.3)</td>
<td>0.36</td>
</tr>
<tr>
<td>NCS</td>
<td>4 (26.7)</td>
<td>12 (44.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>LTRA</td>
<td>5 (33.3)</td>
<td>4 (14.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.4 (13.6;19.4)</td>
<td>16.1 (14.0;26.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>C-ACT score</td>
<td>19 (8;26)</td>
<td>23 (11;27)</td>
<td>0.24</td>
</tr>
<tr>
<td>Baseline FEV₁₀.₅ (% predicted)</td>
<td>73.1 ± 9.0</td>
<td>85.8 ± 15.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline FEV₁ (%)</td>
<td>77.8 ± 10.7</td>
<td>91.5 ± 14.6</td>
<td>0.00</td>
</tr>
<tr>
<td>Maximum decrease in FEV₁₀.₅ (%)</td>
<td>42.2 ± 11.3</td>
<td>21.7 ± 6.3</td>
<td>0.00</td>
</tr>
<tr>
<td>Nadir t (minutes)</td>
<td>2 (0.7)</td>
<td>2 (1.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Increase FEV₁₀.₅ during exercise (%)</td>
<td>0 (0.23)</td>
<td>4 (0;20)</td>
<td>0.30</td>
</tr>
<tr>
<td>Decrease in FEV₁₀.₅ at 15 min [recovery (%)]</td>
<td>15.4 (36.9;0)</td>
<td>5.9 (18.5;0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean heart rate during exercise</td>
<td>84.4 ± 7.0</td>
<td>87.0 ± 4.7</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Results expressed as medians (minimums;maximums), mean values ± SDs, or numbers (percentages). Values in italics are statistically significant. Note: One child was not classified because of early exercise termination (4 minutes) because of dyspnea with signs of breakthrough EIB, but no breakthrough was determined. SABA, short-acting β₂-agonist; LABA, long-acting β₂-agonist (in combination therapy); ICS, inhaled corticosteroid; NCS, nasal corticosteroid; LTRA, leukotriene receptor antagonist; BMI, body mass index; C-ACT, childhood asthma control test; FEV₁₀.₅, forced expiratory volume in 1 second; FEV₁, forced expiratory volume in 0.5 second. * as indicated by a positive IgE test result to inhaled allergens. ** allergy screening in 22 of 27 children.

Figure 2. Mean ± SD FEV₁₀.₅ during and after exercise (N =43) as a percentage of baseline. * administration of 100 µg of salbutamol.
To our knowledge, this study is the first investigating FEV\(_{0.5}\) during exercise in young children aged 5 to 7 years with asthma. Remarkably, we observed that in 36% of the children with EIB, FEV\(_{0.5}\) decreased during exercise of 6 minutes’ duration and within 2 minutes in some children. Breakthrough EIB, which was earlier defined as a 15% decrease in FEV\(_1\) during exercise, has been described both in asthmatic children aged 8 to 15 years and in adults, occurring 6 to 10 minutes and 15 minutes, respectively, after the start of exercise and before cessation of exercise\(^{10,19}\). Comparing the characteristics of children with or without breakthrough EIB shows that breakthrough EIB generally is accompanied by a more severe decrease in FEV\(_{0.5}\) and a slower recovery from EIB, indicating uncontrolled asthma.

**DISCUSSION**

Figure 3. Mean ± SD FEV\(_{0.5}\) during and after exercise in subjects with breakthrough EIB (ie, ≥13% decrease in FEV\(_{0.5}\) during exercise and sustained after exercise (N = 15); lower graph) and non-breakthrough EIB (ie, ≥13% decrease in FEV\(_{0.5}\) after exercise (N = 27); upper graph). A, Percentage of baseline. B, Percent predicted. * administration of 100 µg of salbutamol.
Vilozni et al. documented EIB in young children, measuring pulmonary function after a free-run test, but had a test failure percentage of 14.7%. They described that duration of running is limited by age, and indeed, forced running might be overwhelming in this young age group. An ECT should be sustainable, safe, and enjoyable, and heart rate during exercise should be reasonably maintained at greater than 80% of predicted maximum value. Therefore we chose to use a jumping castle.

The pattern of EIB in young children has been investigated in several studies, showing that it changes with age. The younger the child, the shorter the time to maximal bronchoconstriction after exercise and the quicker the recovery from EIB. Our results confirm this rapid decrease in FEV$_{0.5}$ after exercise; maximum decrease in pulmonary function was at a median of 2 minutes after exercise.

Some remarks can be made about our study. During the ECT, exercise was briefly interrupted twice to perform spirometry. One can argue that an interruption of exercise could influence the decrease in FEV$_{0.5}$ after exercise. However, heart rate monitoring showed unchanged tachycardia, presumably accompanied by unchanged hyperpnea, which is the stimulus for EIB. Despite the interruption, many children had a positive ECT result.

In our ECT protocol spirometry was performed for 15 minutes after cessation of exercise, which is rather short compared with other ECT protocols. We considered this shortened schedule more appropriate because young asthmatic children quickly recover from EIB and easily fatigue as a result of repeated forced breathing manoeuvres.

EIB and breakthrough EIB were defined as an exercise induced decrease in FEV$_{0.5}$ of 13% or greater from baseline value. According to Vilozni et al., FEV$_{0.5}$ is a better index than FEV$_{1}$ for describing EIB in young children, and we would agree with this. The 13% cutoff value was chosen according to Vilozni et al. and Godfrey et al. Defining EIB as a decrease in FEV$_{0.5}$ of 10% or greater from baseline, 3 more children would have had breakthrough EIB and 4 more children would have been given a diagnosis of EIB. When using a 15% or greater decrease as the cutoff value, 2 children would not have been given a diagnosis of breakthrough EIB, and 3 children would not have been given a diagnosis of EIB.

Our results have important clinical implications. First, the rapid onset of EIB in young asthmatic children results in dropping out of exercise, which compromises quality of life, cardiovascular condition and motor development. Secondly, clinicians should be aware that rapid deterioration of performance in young children can be caused not only by poor cardiovascular fitness but also by EIB. Another implication of our study is the limited value of reported history and symptoms for the evaluation of asthma in young children. Exercise induced wheezing, which is specific for EIB, was only observed in a small minority of children with EIB. Most children with EIB experienced coughing, but as with adult athletes, this symptom appeared not to be specific for EIB. Also, we observed no difference between C-ACT score in children with or without EIB, although
C-ACT scores tended to be lower in children with breakthrough EIB. Although the C-ACT is a validated questionnaire assessing asthma control and has proved to be a complementary tool in the follow-up of asthmatic children, one must be careful interpreting this score because it can underestimate the proportion of children with uncontrolled asthma\textsuperscript{14,18,25}.

In conclusion, an ECT using a jumping castle is suitable for diagnosing EIB in young children and has advantages over other kinds of exercise when it comes to safety and efficacy. Our ECT showed that young asthmatic children can experience bronchoconstriction in the first few minutes of exercise. This breakthrough EIB is a predictor for severe EIB and has important clinical implications.
REFERENCES


