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

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Chapter 2

Monitoring pulmonary function during exercise

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ABSTRACT

Rationale
Exercise-induced bronchoconstriction (EIB) is defined as an acute, reversible bronchoconstriction induced by physical exercise. There is a widely held belief that EIB occurs after exercise. However, in asthmatic children the time to maximal bronchoconstriction after exercise is short. This suggests that the onset of EIB in children occurs during exercise. In this study we investigated pulmonary function during exercise in cold air in asthmatic children.

Methods
33 Asthmatic children with a mean age of 12.3 years and a clinical history of exercise induced symptoms, underwent a prolonged, submaximal, exercise test of 12 minutes duration at approximately 80% of the predicted maximum heart rate. Pulmonary function was measured before and every minute during exercise. If EIB occurred (fall in FEV₁ >15% from baseline), exercise was terminated and salbutamol was administered.

Results
19 children showed EIB; in 12 of these children bronchoconstriction occurred during exercise (breakthrough EIB), 7 children showed bronchoconstriction immediately after exercise (non-breakthrough EIB). Breakthrough EIB occurred between 6 and 10 minutes of exercise (mean 7.75 minutes).

Conclusion
In the majority of children with EIB we studied (i.e. 12 out of 19), bronchoconstriction started during, and not after, a submaximal exercise test.
INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is a common manifestation in children and adolescents with asthma and is associated with an impaired quality of life. EIB is defined as an acute, reversible bronchoconstriction occurring 5-15 minutes after cessation of physical exercise. EIB is suggested to be caused by exercise induced drying of the respiratory mucosa, leading to degranulation of mast cells and the subsequent release of inflammatory mediators. These mediators interact with effector cells such as smooth muscle cells and lead to bronchoconstriction. Another proposed mechanism for EIB is that exercise induced hyperpnea causes airway cooling. After exercise, when hyperpnea ceases, the airways rapidly rewarm, leading to engorgement of the hyperplastic vascular bed in the asthmatic airway wall and subsequent bronchoconstriction (thermal hypothesis). Exercise also induces the release of several bronchodilating mediators, such as prostaglandin PGE\(_2\) and nitric oxide, protecting against bronchoconstriction. In addition, exercise induced deep inspirations lead to an increased mechanical stretch of the airway smooth muscle, bronchodilating the lower airways. Indeed exercise is a potent bronchodilator once bronchoconstriction has set in. Thus a balance between bronchoconstrictor and bronchodilator influences exists, preventing EIB during exercise. However, several studies in asthmatic adults demonstrated that prolonged exercise (>15 minutes) can trigger EIB during exercise. Previous studies have shown that the time to maximal bronchoconstriction after exercise is shorter in asthmatic children than in asthmatic adults. This rapid fall of FEV\(_1\) after exercise leads us to hypothesize that EIB in asthmatic children starts during exercise, contrary to the widely held belief that EIB occurs after exercise. The aim of the present study was to investigate pulmonary function during exercise in cold air in asthmatic children.

METHODS

Subjects

Thirty three children (23 male, 10 female) with a mean age of 12.3 years (range 8-15) and with a clinical history of exercise induced symptoms were investigated in this study. Exercise tests were performed as a part of the routine clinical evaluation, though with addition of spirometry during exercise. No short- and long acting bronchodilators were used respectively 8 and 24 hours before testing. None of the children used oral steroids at least 3 weeks before the study. Inhaled corticosteroids and leukotriene antagonists were not withheld before testing. All of the children were informed and the local Ethics Committee was consulted, who filed no objection to perform the study.
Pulmonary function measurements
The children underwent an extensive evaluation of their asthma, which consisted of an exercise provocation challenge, the Asthma Control Questionnaire by Juniper (ACQ) and measurement of the Fraction of the exhaled Nitric Oxide (FeNO), using the miniNIOX®.

Standard lung function tests were performed before, during and after exercise, using a Microloop MK8 Spirometer (ML3535). Before exercise, spirometry consisted of a duplicated full flow volume curve, using standard ERS protocol14. The best value for FEV₁ was used for analysis. During and after exercise spirometry was limited to a single flow volume curve. Only technically correct flow volume curves were used for statistical analysis.

Exercise provocation challenge
After baseline spirometry, a prolonged exercise test was performed by running with nose clipped on a treadmill with an incline of 10% (Horizon® fitness Ti22). Cold, dry air with a temperature of 9.5-10.0°C and humidity of 57-59% (5.5-6.0 mg H₂O/l) was obtained while testing in the local skating rink, IJsbaan Twente, Enschede, Netherlands. Resurfacing of the ice was done with electric driven resurfacing machines. During the test, heart rate was continuously monitored by a radiographic device (Inventum SH 40). The children performed a constant-load exercise test at approximately 80% of the predicted maximum heart rate (210-age)15. During the exercise challenge single flow volume curves were recorded every minute. The maximum duration of the exercise test was 12 minutes or until a fall in FEV₁>15% from baseline value had occurred. In this case the challenge was terminated, one flow volume curve was measured 1 minute after cessation and salbutamol 100 µg was administered immediately after spirometry or at request. In children who completed 12 minutes of exercise, spirometry was obtained at t=1, 3 and 5 minutes after exercise. If EIB (fall in FEV₁>15%) occurred in this period, salbutamol 100 µg was administered immediately after this measurement. To establish recovery, one flow volume curve was measured approximately 10 minutes after administration of salbutamol.

Statistical analysis
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. The level of significance was set at 0.05 (95% confidence intervals (CI)). Between-group comparison of continuous data was performed by ANOVA or Kruskal Wallis tests as appropriate, post hoc test for statistically significant differences was performed with the Tukey’s HSD test. Comparison of nominal or ordinal variables were performed by Chi-square tests. SPSS® for Windows® version 15 (IBM, Chicago, IL, USA) was used to perform all analysis.
RESULTS

Thirty three children participated in the study. Two children were not able to complete the test because of incompatibility with test instructions and one child was excluded because of technical problems during the test (heart rate monitor malfunction). Thirty children were included in the analysis. All children were able to perform spirometry during exercise. Flow volume curves were technically acceptable and no signs of fatigue or spirometry-induced bronchoconstriction were observed.

Nineteen children (11 male, 8 female) showed EIB (fall in FEV₁ >15% from baseline value). In 12 of these children (6 male, 6 female) EIB occurred during exercise (breakthrough EIB). Seven children showed EIB immediately after exercise (non-breakthrough EIB). Eleven children did not show EIB.

Baseline characteristics of the children are shown in table 1. Body Mass Index (BMI) was adjusted for age and gender and calculated as SD from the mean (BMI z-score)\textsuperscript{16}. No significant differences were seen between the baseline characteristics of the breakthrough EIB group, the non-breakthrough EIB group and the non EIB group.

Table 1, Baseline characteristics of breakthrough EIB, non-breakthrough EIB and non EIB.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Breakthrough EIB</th>
<th>Non-Breakthrough EIB</th>
<th>Non-EIB</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.6 (8.2;15.3)</td>
<td>12.5 (11.5;14.2)</td>
<td>12.6 (9.3;15.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Male</td>
<td>6 (50)</td>
<td>5 (71)</td>
<td>9 (82)</td>
<td>0.62</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.8 (−0.4;2.4)</td>
<td>0.6 (−1.4;2.2)</td>
<td>0.7 (−0.8;1.3)</td>
<td>0.65</td>
</tr>
<tr>
<td>ICS</td>
<td>12 (100)</td>
<td>6 (86)</td>
<td>8 (73)</td>
<td></td>
</tr>
<tr>
<td>fluticasone 250 µg 2dd</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>beclomethasone 100 µg 2dd</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>budesonide 200 µg 2dd</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ciclesonide 160 µg 1dd</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LABA *</td>
<td>8 (67)</td>
<td>3 (43)</td>
<td>4 (36)</td>
<td>0.32</td>
</tr>
<tr>
<td>budesonide/formoterol 200/6 µg 2dd</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>fluticasone/salmeterol 250/50 µg 2dd</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LTRA</td>
<td>4 (33)</td>
<td>3 (43)</td>
<td>5 (46)</td>
<td>0.83</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>28 (11;84)</td>
<td>31 (14;119)</td>
<td>30 (11;48)</td>
<td>0.66</td>
</tr>
<tr>
<td>ACQ</td>
<td>1.3 (0.3;3.2)</td>
<td>2.0 (1.0;3.2)</td>
<td>1.2 (0.0;1.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>83.3 ± 9.2</td>
<td>86.7 ± 11.7</td>
<td>89.7 ± 12.9</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean HR during exercise</td>
<td>75.7 ± 2.8</td>
<td>78.5 ± 1.6</td>
<td>79.5 ± 2.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

BMI, Body Mass Index; ICS, inhaled corticosteroid; LABA, Long acting bronchodilator agent (*; combination therapy); LTRA, Leukotriene antagonist (montelukast 1 dd 5 mg); FeNO, Fraction exhaled Nitric Oxide; ACQ, Asthma Control Questionnaire; FEV₁, Forced expiratory volume in 1 s; HR, Heart rate (% of maximum). Results expressed as median (minimum;maximum), mean values ± SD or as numbers (percentages).
Chapter 2

Table 2, Individual characteristics of the breakthrough EIB group.

<table>
<thead>
<tr>
<th>Sub</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>BMI z-score</th>
<th>ICS</th>
<th>LABA</th>
<th>LTRA</th>
<th>Baseline FEV$_1$ (% of pred)</th>
<th>Time to ↓FEV$_1$ &gt;15% (minutes)</th>
<th>↓FEV$_1$, at cessation (% from baseline)</th>
<th>↓FEV$_1$, t=1 (% from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F</td>
<td>11</td>
<td>156</td>
<td>1.3</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>81</td>
<td>7</td>
<td>−15</td>
<td>−47</td>
</tr>
<tr>
<td>2 F</td>
<td>8</td>
<td>137</td>
<td>1.2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>91</td>
<td>6</td>
<td>−24</td>
<td>−28</td>
</tr>
<tr>
<td>3 F</td>
<td>9</td>
<td>141</td>
<td>0.1</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>84</td>
<td>6</td>
<td>−23</td>
<td>−54</td>
</tr>
<tr>
<td>4 F</td>
<td>8</td>
<td>132</td>
<td>2.0</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>74</td>
<td>6</td>
<td>−35</td>
<td>−45</td>
</tr>
<tr>
<td>5 M</td>
<td>15</td>
<td>168</td>
<td>1.9</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>89</td>
<td>8</td>
<td>−16</td>
<td>−32</td>
</tr>
<tr>
<td>6 M</td>
<td>12</td>
<td>155</td>
<td>−0.1</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>67</td>
<td>10</td>
<td>−18</td>
<td>−27</td>
</tr>
<tr>
<td>7 F</td>
<td>10</td>
<td>140</td>
<td>1.7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>96</td>
<td>10</td>
<td>−17</td>
<td>−34</td>
</tr>
<tr>
<td>8 F</td>
<td>14</td>
<td>165</td>
<td>−0.4</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>84</td>
<td>8</td>
<td>−15</td>
<td>−34</td>
</tr>
<tr>
<td>9 M</td>
<td>11</td>
<td>138</td>
<td>0.4</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>85</td>
<td>9</td>
<td>−15</td>
<td>−45</td>
</tr>
<tr>
<td>10 M</td>
<td>11</td>
<td>162</td>
<td>0.1</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>69</td>
<td>10</td>
<td>−17</td>
<td>−17</td>
</tr>
<tr>
<td>11 M</td>
<td>13</td>
<td>163</td>
<td>2.4</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>94</td>
<td>6</td>
<td>−15</td>
<td>−21</td>
</tr>
<tr>
<td>12 M</td>
<td>13</td>
<td>175</td>
<td>−0.2</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>85</td>
<td>7</td>
<td>−19</td>
<td>−26</td>
</tr>
</tbody>
</table>

Sub, subject; F, female; M, male; BMI, Body Mass Index; ICS, inhaled corticosteroid; LABA, Long acting bronchodilator agent; LTRA, Leukotriene antagonist; FEV$_1$, Forced expiratory volume in 1 s; Time to ↓FEV$_1$ >15%, time to EIB during exercise; ↓FEV$_1$, at cessation, fall in FEV$_1$ at cessation of exercise; ↓FEV$_1$, t=1, fall in FEV$_1$ 1 minute after exercise.

Individual characteristics of the breakthrough EIB group are shown in table 2. In this group, EIB occurred between 6 and 10 minutes of exercise (mean 7.75 minutes). Mean fall in FEV$_1$ 1 minute after cessation of exercise was 34% from baseline (range 17-54%). Mean heart rate during exercise (calculated from the second minute of exercise) is shown in table 1. There is a significant difference in mean heart rate between the breakthrough EIB group and non EIB group (75.7% ± 2.8 vs 79.5% ± 2.9, p<0.01; CI:1.0-6.5%).

The pattern observed in most of the subjects of the breakthrough EIB group was an initial increase in FEV$_1$ during the first minutes of exercise. After a short plateau, FEV$_1$ progressively decreased, followed by a steeper fall of FEV$_1$ after exercise, as shown in figure 1. Figure 2 shows the response of FEV$_1$ during exercise in the non-breakthrough EIB group. After an initial increase in FEV$_1$, most children showed a slow decline in FEV$_1$ during the exercise challenge. Mean fall in FEV$_1$ 1 minute after cessation of exercise was 21% from baseline (range 17-34%).

DISCUSSION

The main result of this study is that in the majority of children with EIB (i.e. 12 out of 19) the onset of bronchoconstriction is during submaximal exercise in cold air.

To our knowledge this study is the first to evaluate pulmonary function, as measured by FEV$_1$, during an exercise challenge in cold air in asthmatic children. Several studies have
described bronchoconstriction in asthmatic adults during and after exercise. Rundell et al investigated EIB during exercise in cold air. They found that bronchoconstriction (defined as a fall >10% in FEV₁) occurs in adult athletes during prolonged exercise (~42 minutes) at 90-100% of maximum heart rate¹⁰. Beck and Suman et al studied pulmonary function (FEV₁) in asthmatic adults during different prolonged exercise protocols in laboratory settings and
both observed bronchoconstriction during exercise after about 15 minutes of exercise\textsuperscript{2,6,8,9}. Few studies measured peak expiratory flow rate (PEFR) during exercise in asthmatic children and described that in up to 51.7% of asthmatic children PEFR falls below prechallenge value at the end of a 6-8 minutes exercise challenge, suggesting that EIB occurs frequently during exercise\textsuperscript{17-19}.

The mechanism of bronchoconstriction during exercise could be an imbalance between bronchodilator and bronchoconstrictor influences. During exercise, hyperpnea causes drying and hyperosmolarity of the respiratory mucosa, leading to the release of inflammatory mediators and subsequent bronchoconstriction\textsuperscript{4}. Simultaneously exercise has a bronchodilating potential, caused by the release of Nitric Oxide and prostaglandin PGE\textsubscript{2} and the increased mechanical stretch of the airway smooth muscle through deep inspirations\textsuperscript{6}. Studies in adult asthmatics describe a pattern of an initial bronchodilatation during exercise. After achieving a steady state of about 15 minutes, the constrictor stimulus prevails, with an additional constriction post-exercise\textsuperscript{2,6,7,11}. In asthmatic children we observed the same pattern, however the timing of the events is markedly faster than in adults. The bronchodilator effect of exercise is transient in children and rapidly followed by bronchoconstriction within minutes. This fast pattern may be due to the twitchiness of young airways. The contribution of muscle spasm in the mechanism of EIB in asthmatic children may be relatively high compared to adults. This can also explain their quick recovery of pulmonary function after maximal bronchoconstriction\textsuperscript{12}. Another explanation for EIB during exercise in children may be a failure of bronchodilator influences to counterbalance the bronchoconstrictor influences. Indeed only 2 children were able to fully maintain their FEV\textsubscript{1} during exercise.

Our observation that EIB starts during a relatively short period of exercise in the majority of asthmatic children implies that the thermal hypothesis about the pathophysiology of EIB cannot be sustained in asthmatic children. According to this hypothesis EIB is caused by rapid rewarming of the airways at the cessation of exercise induced hyperpnea\textsuperscript{5}. Anderson et al questioned this hypothesis in 1989, as they observed a fall in PEFR in asthmatic children during exercise\textsuperscript{18}.

Several remarks can be made about this study. Subjects performed an exercise challenge at approximately 80% of their maximum heart rate. According to the ATS guidelines for diagnosing EIB, the intensity of exercise should be set at a heart rate of 80-90% of maximum. Testing at a relatively low exercise intensity probably underestimates the prevalence and severity of EIB\textsuperscript{13,20}. We purposely chose an exercise intensity of 80% of maximum heart rate, since spirometry is easier to perform and a prolonged test easier to sustain during submaximal exercise. Retrospectively mean heart rate during exercise was significantly lower in the breakthrough EIB group compared to the non EIB group (75.7% vs 79.5%). We considered this difference was clinically not relevant and did not cause breakthrough EIB (heart rate was even slightly lower in the breakthrough EIB group). Although we successfully titrated the intensity of exercise to approximately 80% of the predicted maximum heart rate in all children, the
duration of exercise in the non EIB group was longer and heart rate increased steadily during exercise, explaining the difference in mean heart rate.

Another comment can be made about the duration of the exercise test, which differs from regular exercise tests. Given that there is an initial bronchodilatation during the first few minutes of exercise, a standardised protocol of 6 minutes could be too short to document a significant fall FEV₁ during exercise. Therefore, we chose a 12 minutes exercise protocol, as most children show a rapid fall in FEV₁ directly after a regular exercise challenge of 6-8 minutes. Also, a submaximal prolonged test mimics real life exercise in play and sports. Indeed we observed EIB in the majority of children during these 12 minutes. Moreover, the average time for EIB to occur was 7.75 minutes of exercise. Defining EIB as a fall in FEV₁ >10% from baseline, instead of >15%, 5 more children would have had a positive breakthrough test (i.e. 17 out of 19).

One could argue that the observed fall in FEV₁ during exercise is a result of submaximal effort or respiratory muscle fatigue. However, all children performed technically adequate flow volume curves during exercise, whether or not there was a fall in FEV₁.

Eleven children did not show EIB. This might be due to the fact that self reported exercise induced symptoms are not always caused by EIB. Furthermore, we measured FEV₁ to a maximum of 5 minutes post-exercise, which may underestimate the incidence of EIB as the time to maximal bronchoconstriction after exercise is between 2 and 12 minutes. However the majority of children reach maximal bronchoconstriction in the first 5 minutes post-exercise.

The fact that bronchoconstriction can occur early during exercise in asthmatic children is of clinical importance. Not only can it compromise the athletic performance of the child but it can also influence a child’s attitude to exercising. Dropping out during exercise lowers self esteem and leads to avoidance of exercise and consequently deterioration of cardiovascular condition.

Monitoring pulmonary function in asthmatic children during exercise was feasible in our study and has benefits. It prevents severe and uncontrolled falls in FEV₁ that can occur during and after a regular exercise challenge to measure EIB. Furthermore a breakthrough test could potentially be used as a dose response test, in which time to the occurrence of EIB can be considered as the degree of airway hyperresponsiveness.

In conclusion, measuring pulmonary function during exercise in asthmatic children shows that the bronchoprotective effect of exercise is short-lived in children and that EIB frequently starts during, and not after, submaximal exercise. Moreover it may provide complementary clinical information, as breakthrough EIB leads to serious compromise of participation in active play and sports and indicates uncontrolled asthma, for which appropriate therapy measures are needed. More research needs to be done to characterise asthmatic children susceptible to airway obstruction.
REFERENCES