Exercise induced airway obstruction in children: Patho-physiology and diagnostics
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Chapter 4

Inspiratory airflow limitation after exercise challenge in cold air

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ABSTRACT

Rationale
Methacholine and histamine can lead to inspiratory flow limitation in asthmatic children and adults. This has not been analyzed after indirect airway stimuli, such as exercise. The aim of the study was to analyze airflow limitation after exercise in cold, dry air.

Methods
72 asthmatic children with mild to moderate asthma (mean age 13.2 ± 2.2 yrs) performed a treadmill exercise challenge. A fall of >10% in FEV₁ was the threshold for expiratory flow limitation and a fall of >25% of MIF₅₀ was the threshold for inspiratory flow limitation. The occurrence of wheeze, stridor and cough were quantified before and after exercise.

Results
After exercise, the mean fall in FEV₁ was 17.7 ± 14.6%, while the mean fall in MIF₅₀ was 25.4 ± 15.8%; no correlation was found between fall in FEV₁ and MIF₅₀ (R²: 0.04; p=0.717). 53 of the 72 children showed an inspiratory and/or expiratory airflow limitation. 38% (20/53) of these children showed an isolated expiratory flow limitation, 45% (24/53) showed both expiratory and inspiratory flow limitation and 17% (9/53) showed an isolated inspiratory flow limitation. The fall in FEV₁ peaked 9 minutes after exercise and correlated to expiratory wheeze. The fall in MIF₅₀ peaked 15 minutes after exercise and correlated to inspiratory stridor. The time difference in peak fall between FEV₁ and MIF₅₀ was statistically significant (5.9 minutes; p<0.001, 99% CI: 2.3 - 9.5 minutes).

Conclusion
This study shows that an exercise challenge in asthmatic children can give rise to inspiratory airflow limitation, which may give rise to asthma like symptoms.
INTRODUCTION

Asthma is a common, chronic disease in which indirect stimuli such as exercise may lead to transient narrowing of the lower airways resulting in an expiratory flow limitation (EIB)\(^1\). A direct stimulus such as methacholine may lead to inspiratory as well as expiratory flow limitation in asthmatic children and adults\(^2\)-\(^4\). It has been hypothesized that this inspiratory flow limitation is the result of chronic inflammation of the upper airways, a frequent co-morbidity in childhood asthma\(^5\).

In asthmatic children, exercise may also lead to symptoms mimicking EIB\(^6\),\(^7\). Vocal cord dysfunction (VCD) may lead to many exercise induced symptoms and can easily be mistaken for EIB\(^8\). In most cases of VCD exercise induced symptoms, such as stridor and acute 'choking' occur during exercise\(^9\). In field observations however, inspiratory stridor and dyspnoea may be present in asthmatic children well after exercise. We propose that an indirect challenge such as exercise may cause inspiratory airway obstruction like methacholine and histamine, mimicking asthma like symptoms.

The aim of the study was to analyze airflow limitation after exercise in cold, dry air.

MATERIALS AND METHODS

Study design
Open, cross sectional design. All exercise challenge tests were performed between January 1\(^{\text{st}}\) 2005 and April 1\(^{\text{st}}\) 2008.

Subjects
Seventy-two children (mean age 13.2 ± 2.2 yrs) with mild to moderate asthma with exercise induced dyspnoea were selected from the paediatric outpatient clinic of Medisch Spectrum Twente Hospital. Most patients had a history of allergy and 65 completed a radioallergosorbent test (RAST). Subjects were required to withhold the use of long acting bronchodilators for 24 hours and the use of short acting bronchodilators for 8 hours prior to the tests. No vigorous exercise was permitted for 4 hours prior to the exercise challenge. The internal review board (Medisch Ethische Toetsings Commissie of the Medisch Spectrum Twente) filed no complaint to perform the study.

Exercise challenge
Exercise testing was performed on a treadmill (Reebok\(^\circ\), TR1 premium run, Canton, MA, USA) according to ATS/ERS recommendations\(^10\). The exercise challenges were performed in the local ice skating rink, to obtain cold air (2-5°C, 1-5 mg∙l\(^{-1}\) H\(_2\)O). Children ran, nose clipped, on a treadmill with a 10 degree slope, for a 4 minute period with a heart rate at 90 percent of
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predicted maximum (210-age) after an acclimatization period of 2 minutes\textsuperscript{10,11}. The total exercise time was 6 minutes. Heart rate was monitored with a Polar Sport tester (Polar Electro®, Finland). A single observer (JD) quantified respiratory wheeze, inspiratory stridor and cough using auscultation\textsuperscript{12}.

**Asthma Control Questionnaire**

The asthma control questionnaire (ACQ) developed by Juniper and colleagues is a reliable and validated instrument to measure asthma control\textsuperscript{13}. All children completed the original Dutch version of the ACQ before exercise. Responses were given on a 7-point scale and the overall score is the mean of 6 questions, with the question of the FEV\textsubscript{1} omitted. Well-controlled asthma was defined by an ACQ of less than 0.75 and uncontrolled asthma by an ACQ of more than 1.50; an ACQ between 0.75 and 1.49 was seen as an indifferent control of asthma\textsuperscript{14}.

**Pulmonary Function Measurements**

A Masterscope® Jaeger®, (IBM PS 235X; Jaeger, Würzburg, Germany) was used to measure lung volumes and flow-volume loops. This spirometer was calibrated on the morning of each study day. The flow-volume loop was recorded using ATS/ERS guidelines. After exercise flow volume loop measurements were repeated in duplex at 1, 3, 6, 9, 12, 15, 20 and 25 minutes. Pulmonary function was calculated from the best curve.

The best forced expiratory volume in the first second (FEV\textsubscript{1}) value was used for analysis of the expiratory airflow limitation and Zapletal reference values were used to calculate the predicted value of the FEV\textsubscript{1}\textsuperscript{15}. A fall of more than 10% in FEV\textsubscript{1} was considered positive for expiratory flow limitation, as recommended by the ATS-ERS guidelines when evaluating EIB in a research setting\textsuperscript{10}.

The best maximal mid inspiratory flows (MIF\textsubscript{50}), reaching a plateau and accompanied by a forced inspiratory vital capacity of more than 80% of baseline, were used to evaluate inspiratory flow limitation. A fall of more than 25% of MIF\textsubscript{50} was considered positive for inspiratory flow limitation\textsuperscript{4,5}. Tomalek reference values were used to calculate the predicted value of the MIF\textsubscript{50}\textsuperscript{16}.

**Statistical analysis**

Results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (range) for non-normal data or as numbers with corresponding percentages if nominal or ordinal. Because of the large number of tests, we chose to set the level of significance at 0.01 (99% confidence intervals (CI)). To identify variables that were associated with inspiratory and expiratory flow limitation, unpaired t-tests or Mann-Whitney U tests were performed as appropriate. Between-group comparisons 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 analyses.
RESULTS

Seventy-two children with mild to moderate asthma performed an exercise challenge test in cold air. Baseline characteristics of the patients are shown in table 1.

After exercise, the mean fall in FEV₁ was 17.1 ± 14.7%, while the mean fall in MIF₅₀ was 25.8 ± 16.1%. When plotting the fall in FEV₁ against the fall in MIF₅₀, no correlation was found (R²: 0.04; p=0.717), as can be seen in figure 1.

Using the cut-off points as stated before (fall in FEV₁ of more than 10% and fall in MIF₅₀ of more than 25%) patients were divided into 4 subgroups, as can be seen in table 2. It is remarkable that of the children without a significant fall in FEV₁, almost half (9/19) showed a significant fall in MIF₅₀, additionally, of the children without a significant fall in MIF₅₀, almost half (20/39) showed a significant fall in FEV₁.

After exercise, 74% of the patients showed a flow limitation (53/72). Of these, 38% (20/53) showed an isolated expiratory flow limitation, 45% (24/53) an expiratory and inspiratory flow limitation, and 17% (9/53) showed an isolated inspiratory flow limitation. The mean time to maximum fall in FEV₁ was 9.2 ± 7.6 minutes after exercise, while the mean time to maximum

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**Table 1.** Baseline characteristics. Data are given in mean ± SD or numbers (percentage)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.2 ± 2.2</td>
</tr>
<tr>
<td>Male Gender</td>
<td>48 (67)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 9</td>
</tr>
<tr>
<td>FEV₁ (% of predicted)</td>
<td>101.4 ± 9.5</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>83.4 ± 16.5</td>
</tr>
<tr>
<td>MIF₅₀ (% of predicted)</td>
<td>129.7 ± 28.6</td>
</tr>
<tr>
<td>ICS</td>
<td>57 (79)</td>
</tr>
<tr>
<td>ICS + LABA</td>
<td>44 (61)</td>
</tr>
<tr>
<td>NCS</td>
<td>19 (26)</td>
</tr>
<tr>
<td>ACQ ≤ 0.75</td>
<td>38 (54)</td>
</tr>
<tr>
<td>0.75 &lt; ACQ &lt; 1.50</td>
<td>20 (29)</td>
</tr>
<tr>
<td>ACQ ≥ 1.50</td>
<td>12 (17)</td>
</tr>
<tr>
<td>House Dustmite Allergy</td>
<td>43 (60)</td>
</tr>
<tr>
<td>Grass - Tree pollen Allergy</td>
<td>38 (53)</td>
</tr>
<tr>
<td>Food Allergy</td>
<td>14 (19)</td>
</tr>
</tbody>
</table>

The fall in MIF $50$ was $15.1 \pm 7.9$ minutes after exercise (Difference 5.9 minutes; $p<0.001$, 99% CI: 2.3 - 9.5 minutes). The inspiratory and expiratory airflow in time for each group can be seen in figure 2.

The use of inhaled corticosteroids was not related to the occurrence of EIB (chi-square $p=0.573$) or inspiratory flow limitation (chisquare $p=0.367$). Similarly, the use of nasal corticosteroids was not related to the occurrence of EIB (chi-square $p=0.528$ or inspiratory flow limitation (chisquare $p=0.457$), suggesting that the use of inhaled or nasal corticosteroids did not significantly effect the likelihood for EIB or inspiratory flow limitation in asthmatic children.

The correlation between the overall ACQ and fall in FEV$_1$ after exercise was 0.12 ($p=0.864$) and the correlation with the fall in MIF $50$ was 0.18 ($p=0.810$). When dividing the patients into groups by the asthma control cut-offs provided by Juniper et al., omitting the last question. There was no correlation with fall in FEV$_1$ ($p=0.077$) nor with fall in MIF $50$ ($p=0.126$) as can be seen in table 3.
Figure 2. Expiratory flow limitation and Inspiratory flow limitation over time for each group of patients: 1) No flow limitation; 2) Isolated expiratory flow limitation; 3) Isolated inspiratory flow limitation and 4) Both expiratory and inspiratory flow limitation.

FEV₁: Forced expiratory volume in one second; MIF₅₀: Mid inspiratory Flow.

Table 3. Subdivision of patients for control of asthma as measured with the ACQ versus fall in FEV₁ and MIF₅₀.

<table>
<thead>
<tr>
<th></th>
<th>Well-controlled</th>
<th>Indifferent</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACQ &lt; 0.75</td>
<td>ACQ 0.75-1.49</td>
<td>ACQ ≥ 1.50</td>
</tr>
<tr>
<td></td>
<td>n = 38</td>
<td>n = 20</td>
<td>n = 12</td>
</tr>
<tr>
<td>Fall in FEV₁ greater than 10%</td>
<td>14 (37)</td>
<td>5 (25)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Fall in FEV₁ after exercise</td>
<td>17.2 ± 15.8</td>
<td>12.2 ± 5.9</td>
<td>24.4 ± 19.9</td>
</tr>
<tr>
<td>Fall in MIF₅₀ greater than 25%</td>
<td>16 (42)</td>
<td>10 (50)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Fall in MIF₅₀ after exercise</td>
<td>22.1 ± 17.7</td>
<td>30.9 ± 19.1</td>
<td>28.7 ± 14.5</td>
</tr>
</tbody>
</table>

FEV₁: Forced expiratory volume in one second; MIF₅₀: Mid inspiratory Flow. ACQ: Asthma Control Questionnaire.

Table 4. The occurrence of wheeze, stridor and cough compared to the maximum fall in FEV₁ and MIF₅₀.

<table>
<thead>
<tr>
<th></th>
<th>Fall in FEV₁ (% of baseline)</th>
<th>Fall in MIF₅₀ (% of baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Wheeze</td>
<td>22.6 ± 17.1</td>
<td>11.0 ± 6.0</td>
</tr>
<tr>
<td>Stridor</td>
<td>19.4 ± 15.7</td>
<td>13.0 ± 11.7</td>
</tr>
<tr>
<td>Cough</td>
<td>19.0 ± 15.8</td>
<td>10.4 ± 4.7</td>
</tr>
</tbody>
</table>
Figure 3. FEV₁ and MIF₅₀ in % fall over time, for children with and without wheeze.

FEV₁: Forced expiratory volume in one second; MIF₅₀: Mid inspiratory Flow.
* Marks significant differences (p≤0.01)

Figure 4. FEV₁ and MIF₅₀ in % fall in time, for children with and without stridor.

FEV₁: Forced expiratory volume in one second; MIF₅₀: Mid inspiratory Flow.
* Marks significant differences (p≤0.01)
Open marker indicates n<10
The occurrence of expiratory wheeze and cough were linked with a fall in FEV₁, while the occurrence of inspiratory stridor was linked with a fall in MIF₅₀, as can be seen in table 4.

The relation over time between spirometry and wheeze, stridor and cough can be seen in figure 3, 4 and 5 respectively.

**DISCUSSION**

This study shows that exercise can induce inspiratory flow limitation as well as expiratory flow limitation in asthmatic children. Inspiratory flow limitation was related to an inspiratory stridor but unrelated to the occurrence or severity of expiratory flow limitation.

Exercise induced inspiratory stridor and flow limitation is most commonly attributed to VCD. VCD is a heterogeneous entity and as such the inspiratory flow limitation we observed might have been attributed to VCD. Laryngoscopy during and immediately after exercise and not lung-function is considered to be the gold standard to diagnose VCD. However the inspiratory flow limitation we observed peaked well after ceasing exercise and was not accompanied by acute 'choking', both of which are not compatible with a diagnosis of VCD and suggest another cause.
Methacholine and histamine have also been known to cause inspiratory flow limitation, mimicking asthma like symptoms, in both children² and adults³⁴. Rolla et al. found inflammation of the laryngeal mucosa in patients with methacholine induced inspiratory flow limitation and hypothesized that this was due to chronic mouth breathing as a result of chronic upper airway inflammation²⁹. Turktas et al. observed that the responsiveness to methacholine measured with the MIF₅₀ subsided after appropriate treatment of upper airway co-morbidity². Although the majority of asthmatic children have an upper airway inflammation⁵, we did not find a lower prevalence of inspiratory airflow limitation in children using nasal corticosteroids. We propose this is due to a limited medication adherence.

Several remarks should be made about this study. Analysis of the inspiratory flow limb is difficult, especially in children. The MIF₅₀ can be used to analyze inspiratory flow limitation in children¹⁶,²⁰ and Tomalak and co-workers have calculated reference values for children¹⁶. The observed mean pre-exercise MIF₅₀ was approximately 1 standard deviation above predicted, which indicates that the children in our study were capable of performing technically acceptable flow volume loops. To accurately analyze the inspiratory limb, three repeated inspiratory limbs are required for analysis²¹. Although feasible before exercise, the time schedule after exercise forced the use of duplex flow volume loops. A reduction of the inspiratory vital capacity could be accompanied by a higher peak and mid inspiratory flow and a reduction of the plateau phase of the curve. To avoid artificially deviant MIF₅₀ values, and to increase the accuracy of the analysis, the maximal MIF₅₀ was chosen when accompanied by a forced inspiratory vital capacity of more than 80% of baseline and reaching a plateau phase¹⁶.

We choose to use the fall in MIF₅₀ to analyze the inspiratory flow limitation similar to studies using direct challenges. One cannot copy the rate of decline in flow limitation used in direct provocation to indirect provocation. As the cut-off for expiratory flow limitation used is typically higher in direct challenges than in indirect challenges, we believe using the same cut-offs for inspiratory flow-limitation in indirect challenges is sensible. We did not use the fall in the MIF₅₀/MEF₅₀ ratio, as MEF₅₀ fell considerably in most children.

We compared the changes in inspiratory airflow limitation in the different groups with the group of asthmatic children without exercise induced airflow limitation. The pattern of inspiratory airflow limitation is unknown in healthy children. However, in the group in which we did not observe airflow limitation, airway inflammation was apparently well controlled. Allowing comparison between the groups with different flow patterns.

Clinical signs, i.e. cough, wheeze and stridor, were analyzed by a single observer (JD), which might have given rise to observer bias. However the strong association between wheezing and expiratory flow limitation and stridor and inspiratory flow limitation warrents the use of these symptoms for diagnosis.
Inspiratory flow limitation after exercise

The ACQ can be used to assess control of asthma and exercise induced symptoms (question 3)\textsuperscript{13}. We did not find a relation between either expiratory or inspiratory flow limitation after exercise and the outcome of the ACQ. This is in line with previous studies that analyzed the outcome of an exercise challenge of children with exercise induced symptoms\textsuperscript{22}. Seear et al. and Abu-Hassan et al. found that persistent exercise induced symptoms can be due to other causes than expiratory flow limitation\textsuperscript{6,7}. In these studies a definitive diagnosis for the cause of the exercise induced dyspnoea could not be found in a sizable group (21-63%)\textsuperscript{6,7}. We speculate that these cases can be due to an inspiratory flow limitation. Inspiratory flow restriction is closely related to overall perceived dyspnea\textsuperscript{23}. Furthermore, inspiratory flow limitation can compromise effective inhalation of rescue dry powder beta-2-agonists\textsuperscript{24}. The inhalation of dry powder, commonly used by children for EIB in this age group, is dependent on peak inspiratory flow and the ability to sustain inspiratory flow, which are both reduced by inspiratory flow limitation\textsuperscript{25}.

This study shows that an exercise challenge in asthmatic children can give rise to inspiratory as well as expiratory airflow limitation in asthmatic children. Inspiratory airflow limitation is not related to expiratory flow limitation and may give rise to asthma like symptoms after exercise and hamper the effect of inhaled rescue medication. More research should be done to analyze the pathological basis of the observed inspiratory flow limitation.
REFERENCES

Inspiratory flow limitation after exercise