Inspiratory airflow limitation after exercise challenge in cold air in asthmatic children

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KEYWORDS
Airway hyperresponsiveness; Asthma in children; Extrathoracic airway hyperreactivity; Exercise induced asthma

Summary
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.

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.

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 min after exercise and correlated to expiratory wheeze. The fall in MIF50 peaked 15 min after exercise and correlated to inspiratory stridor. The time difference in peak fall between FEV1 and MIF50 was statistically significant (5.9 min; p < 0.001, 99% CI: 2.3–9.5 min).

Abbreviations: EIB, exercise induced bronchoconstriction; VCD, vocal cord dysfunction; RAST, radioallergosorbent test; ACQ, asthma control questionnaire; FEV1, forced expiratory volume in the first second; MIF50, maximal mid inspiratory flow; SD, standard deviation; CI, confidence intervals; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long acting bronchodilating agent; NCS, nasal corticosteroid.

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In 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. © 2012 Elsevier Ltd. All rights reserved.

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). A direct stimulus such as methacholine may lead to inspiratory as well as expiratory flow limitation in asthmatic children and adults. 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.

In asthmatic children, exercise may also lead to symptoms mimicking EIB. Vocal cord dysfunction (VCD) may lead to many exercise induced symptoms and can easily be mistaken for EIB. In most cases of VCD exercise induced symptoms, such as stridor and acute ‘choking’ occur during exercise. 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 1st 2005 and April 1st 2008.

Subjects

Seventy-two children (mean age 13.2 ± 2.2 yrs) with mild to moderate paediatrician diagnosed asthma in accordance with GINA guidelines with exercise induced dyspnoea were selected from the paediatric outpatient clinic of Medisch Spectrum Twente Hospital. Most children used inhaled corticosteroids (79%) and had a history of allergy and 65 completed a radioallergosorbent test (RAST). None of the children were hospitalized for an exacerbation of asthma for at least 6 months prior to testing. Subjects were required to withhold the use of long acting bronchodilators for 24 h and the use of short acting bronchodilators for 8 h prior to the tests. No vigorous exercise was permitted for 4 h prior to the exercise challenge. All testing commenced in the clinical setting and 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®, TR1 premium run, Canton, MA, USA) according to ATS/ERS recommendations. The exercise challenges were performed in the local ice skating rink, to obtain cold air (2–5 °C, 1–5 mg l⁻¹ H₂O). Children ran, nose clipped, on a treadmill with a 10° slope, for a 4 min period with a heart rate at 90 percent of predicted maximum (210-age) after an acclimatization period of 2 min. The total exercise time was 6 min. 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.

The asthma control questionnaire (ACQ) developed by Juniper and colleagues is a reliable and validated instrument to measure asthma control. 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 FEV1 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.

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 min. Pulmonary function was calculated from the best curve.

The best forced expiratory volume in the first second (FEV1) value was used for analysis of the expiratory airflow limitation and Zapletal reference values were used to calculate the predicted value of the FEV1. A fall of more than 10% in FEV1 was considered positive for expiratory flow limitation, as recommended by the ATS-ERS guidelines when evaluating EIB in a research setting.

The best maximal mid inspiratory flows (MIF50), 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 MIF50 was considered positive for inspiratory flow limitation. Tomalek reference values were used to calculate the predicted value of the MIF50.

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 ($R^2$: 0.04; $p$ = 0.717), as can be seen in Fig. 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, after exercise 26% of the patients did not show any flow limitation, while74% 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. 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) an expiratory and inspiratory flow limitation, and

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Value</th>
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<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>

**Table 1** Baseline characteristics. Data are given in mean ± SD or numbers (percentage) FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity, MIF50: Maximal mid inspiratory flow, ICS: Inhaled corticosteroid, LABA: Long acting bronchodilating agent, NCS: Nasal corticosteroid, ACQ: Asthma control questionnaire.

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.

Expiratory 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 could be 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.\textsuperscript{8,9,18,19}

Methacholine and histamine have also been known to cause inspiratory flow limitation, mimicking asthma like symptoms, in both children\textsuperscript{2} and adults.\textsuperscript{3,4} 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 inflammation.\textsuperscript{20} Turktas et al. observed that the responsiveness to methacholine measured with the MIF\textsubscript{50} subsided after appropriate treatment of upper airway co-morbidity.\textsuperscript{2} Although the majority of asthmatic children have an upper airway inflammation,\textsuperscript{5} 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 MIF\textsubscript{50} can be used to analyze inspiratory flow limitation in children\textsuperscript{17,21} and Tomalak and co-workers have calculated reference values for children.\textsuperscript{17} The observed mean pre-exercise MIF\textsubscript{50} 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 analysis.\textsuperscript{22} Although feasible before exercise, the time schedule after exercise forced the use of duplex flow volume loops. The number of forced breathing manoeuvres following exercise might have enhanced the observed flow limitation although we did not see the inspiratory flow limitation in all children. Furthermore, the number of forced breathing manoeuvres in the used protocol is similar to the number of forced breathing manoeuvres required for Methacholine testing reducing the likelihood of a significant effect of fatigue.\textsuperscript{2,3,11} 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 MIF\textsubscript{50} values, and to increase the accuracy of the analysis, the maximal MIF\textsubscript{50} was chosen when accompanied by a forced inspiratory vital capacity of more than 80% of baseline and reaching a plateau phase.\textsuperscript{17}

We choose to use the fall in MIF\textsubscript{50} to analyze the inspiratory flow limitation similar to studies using direct challenges. One cannot copy the rate of decline in flow

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
 & Well-controlled ACQ $< 0.75$ $n = 38$ & Indifferent ACQ $0.75 - 1.49$ $n = 20$ & Uncontrolled ACQ $\geq 1.50$ $n = 12$ \\
\hline
Fall in FEV\textsubscript{1} greater than 10\% & 14 (37) & 5 (25) & 8 (67) \\
Fall in FEV\textsubscript{1} after exercise & 17.2 $\pm$ 15.8 & 12.2 $\pm$ 5.9 & 24.4 $\pm$ 19.9 \\
Fall in MIF\textsubscript{50} greater than 25\% & 16 (42) & 10 (50) & 5 (42) \\
Fall in MIF\textsubscript{50} after exercise & 22.1 $\pm$ 17.7 & 30.9 $\pm$ 19.1 & 28.7 $\pm$ 14.5 \\
\hline
\end{tabular}
\caption{Subdivision of patients for control of asthma as measured with the ACQ versus fall in FEV\textsubscript{1} and MIF\textsubscript{50}. FEV\textsubscript{1}: Forced expiratory volume in 1 s; MIF\textsubscript{50}: Mid inspiratory Flow. ACQ: Asthma control questionnaire.}
\end{table}
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 MIF$_{50}$/MEF$_{50}$ ratio, as MEF$_{50}$ 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 warrants the use of these symptoms for diagnosis.

The ACQ can be used to assess control of asthma and exercise induced symptoms (question 3)$^{14}$. 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.$^{23}$ See et al. and Abu-Hassan et al. found that persistent exercise induced symptoms can be due to other causes than expiratory flow limitation.$^{6,7}$ In these studies a definitive diagnosis for the cause of the exercise induced dyspnoea could not be found in a sizable group (21–63%).$^{6,7}$ We speculate that these cases can be due to an inspiratory flow limitation. Inspiratory flow restriction is closely related to overall perceived dyspnea.$^{24}$ Furthermore, inspiratory flow limitation can compromise effective inhalation of rescue dry powder beta-2-agonists.$^{25}$ 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.$^{26}$

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>p-value</th>
<th>99% CI</th>
<th>Yes</th>
<th>No</th>
<th>p-value</th>
<th>99% CI</th>
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<tbody>
<tr>
<td>Wheeze</td>
<td>22.6±17.1</td>
<td>11.0±6.0</td>
<td>&lt;0.001</td>
<td>2.8–18.4</td>
<td>26.9±16.6</td>
<td>22.6±15.3</td>
<td>0.080</td>
<td>–6.5–15.0</td>
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<tr>
<td>Stridor</td>
<td>19.4±15.7</td>
<td>13.0±11.7</td>
<td>0.048</td>
<td>–3.0–15.7</td>
<td>28.8±16.2</td>
<td>17.0±12.8</td>
<td>&lt;0.001</td>
<td>1.8–21.8</td>
</tr>
<tr>
<td>Cough</td>
<td>19.0±15.8</td>
<td>10.4±4.7</td>
<td>0.001</td>
<td>1.9–15.3</td>
<td>26.2±16.6</td>
<td>20.6±13.5</td>
<td>0.158</td>
<td>–8.0–19.3</td>
</tr>
</tbody>
</table>

**Table 3** The occurrence of wheeze, stridor and cough compared to the maximum fall in FEV$_1$ and MIF$_{50}$.

![Figure 3](image-url) **Figure 3** FEV$_1$ and MIF$_{50}$ in % fall over time, for children with and without wheeze. FEV$_1$: Forced expiratory volume in 1 s; MIF$_{50}$: Mid inspiratory flow. * Marks significant differences ($p \leq 0.01$).

![Figure 4](image-url) **Figure 4** FEV$_1$ and MIF$_{50}$ in % fall in time, for children with and without stridor. FEV$_1$: Forced expiratory volume in 1 s; MIF$_{50}$: Mid inspiratory flow. * Marks significant differences ($p \leq 0.01$) Open marker indicates $n < 10$. 

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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.

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Conflict of interest statement

All authors have no conflict of interest.

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