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

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Chapter 3

Effects of a single dose inhaled corticosteroid on the dynamics of airway obstruction after exercise

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ABSTRACT

Rationale
Exercise-induced bronchoconstriction (EIB) is defined as a transient narrowing of the airways induced by exercise. Repetitive measurements of spirometric parameters, such as FEV\(_1\) and expiratory flows, and FOT measurements can be used to analyze the dynamics of EIB. A single high dose of fluticasone propionate (FP) protects against EIB. The aim of the study was to analyze the effect of FP on the dynamics of exercise induced airway narrowing as measured with FOT and spirometry.

Methods
12 children performed an exercise challenge on 2 separate days, 4 hours after inhalation of 1 mg FP (pressurized metered dose inhaler) or a placebo. Before and after the exercise flow-volume loops as well as the FOT (frequency range: 4-32 Hz) were measured.

Results
The FEV\(_1\), and FEF\(_{50}\) fell significantly after exercise within groups; the peak fall in FEV\(_1\) after FP was significantly smaller than after placebo (respectively 19.3 ± 14.6% and 29.2 ± 14.8%, p=0.03, 95% CI:0.9%-18.8%). The fall in FEV\(_1\) and FEF\(_{50}\) peaked 3 minutes after exercise and showed a subsequent partial recovery. The fall in the FEV\(_1\)/FVC ratio showed a later peak fall (12 minutes after exercise). The resistance increased while the reactance decreased significantly after exercise. FP significantly decreased the maximal increase in Rrs when compared to the placebo (respectively 176.5 ± 59.1% and 201.0 ± 63.8% (p=0.05, 95% CI:0.5%-48.7%). The maximal decrease in Xrs\(_6\) was not significantly affected by FP (p=0.06).

Conclusion
Repetitive spirometric and FOT measurements after exercise show a rapid narrowing and steady recovery of the patency of the conducting airways, and indicate a delayed and prolonged recovery of the smaller airways. A single high dose of inhaled FP seems to employ its effect mainly in the conducting airways.
INTRODUCTION

Childhood asthma is a common disease, which is frequently complicated by exercise induced bronchoconstriction (EIB). EIB is defined as a transient narrowing of the airways induced by exercise. The dynamics of airway narrowing and recovery in EIB are largely unknown. To evaluate EIB the forced expiratory volume in the first second (FEV₁) is routinely used, corresponding with the patency of the larger, conducting airways. Other spirometric indices such as FEF₂₅, FEF₅₀ and FEF₇₅ have been linked with the patency of respectively larger and smaller airways. The forced oscillation technique (FOT) is a sensitive and effort independent technique and can determine airway resistance and reactance. The FOT has been used to evaluate EIB using change in lower frequency resistance and reactance. The lower frequency reactance reflects the capacity of the conducting airways. The lower frequency resistance reflects the capacitive properties of the respiratory system i.e. lung stiffness, intra-parenchymal airway mechanics and airway-parenchyma interdependence. A single high dose of inhaled corticosteroid, such as fluticasone propionate (FP), protects against airway obstruction caused by various indirect challenges such as, exercise, eucapnic voluntary hyperventilation and hypertonic saline. It is unclear where inhaled steroids employ their effects.

The aim of the study was to analyze the effect of fluticasone propionate on the severity and dynamics of exercise induced airway narrowing as measured with FOT and spirometry.

MATERIALS AND METHODS

Study design

The study had a prospective, randomized, double-blind, cross-over, placebo-controlled design. All subjects performed an exercise challenge on 2 separate days receiving either FP or a placebo in a randomized order. Tests were performed within a time interval of at least 6 days and a maximum of 14 days to allow wash-out and minimize periodic effects. Before and after exercise, lung function was measured using FOT followed by flow-volume loops. After the last flow-volume performance, or on patient request, salbutamol was inhaled. Fifteen minutes after inhalation of salbutamol all measurements were repeated as before the exercise challenge.

Subjects

Asthmatic children with a mean age of 14.0 ± 1.2 years were selected from the outpatient clinic of the pediatric department of the Medisch Spectrum Twente and included in the study. All children had self-reported exercise induced dyspnea and 11/12 (92%) children had a positive radioallergosorbent test (RAST). All patients had stable mild to moderate asthma with
no asthma exacerbations or need for oral corticosteroids in the last year before the test. All children were free of oral and inhaled corticosteroids and leukotriene receptor antagonists for at least 4 weeks before the challenges. FEV\textsubscript{1} values before the second exercise challenge had to be within 12% compared to baseline FEV\textsubscript{1} to ensure controlled asthma. The study protocol was evaluated and approved by the medical ethics board of the Medisch Spectrum Twente, Enschede, the Netherlands. All patients and parents signed the written informed consent. The trial has been registered under ISRCTN number: ISRCTN61380683

**Interventions**

Study medication consisted of FP or placebo. Four hours before the exercise challenge, children inhaled 4 actuations of 250 µg FP (Flixotide®, GlaxoWellcome®) using a pressurized metered dose inhaler device in conjunction with a Volumatic® spacer device (GlaxoWellcome®). In all children, inhalation of the study medication occurred under supervision. Patients were instructed to refrain from strenuous activity 4 hours before the exercise challenges. For randomization a linear congruential algorithm of Park and Miller with Bays-Durham shuffling was employed, using block sizes of 2, 4, and 8 children. Exercise challenges were performed in the local skating rink, to obtain cold, dry air (1-5°C; 1.7 mg∙l\textsuperscript{-1} to 4.8 mg∙l\textsuperscript{-1}). The challenges were performed on a treadmill with a 10 degree slope. Children ran for a total of 6 minutes with a 2 minutes period to reach the targeted heart rate of 90 percent of predicted maximum (210-age)\textsuperscript{2}. The nose was clipped to accommodate equal testing circumstances for all subjects. Thirty minutes after the exercise challenge, or earlier on a patient’s request, 400 μg Salbutamol metered dose inhaler was given in conjunction with a spacer device.

**Spirometric measurements**

A Masterscope® Jaeger® (Hoechberg, Germany) was used to measure spirometry. Flow-volume loops were recorded using standard ERS protocol and a fall in FEV\textsubscript{1} of more than 10% was the cut-off value for EIB. Before exercise, flow-volume loops were duplicated. After exercise flow volume loop measurements were repeated in duplex at 1, 3, 6, 9, 12, 15, 20, 25 and 30 minutes. The best values for FEV\textsubscript{1}, FEF\textsubscript{25}, FEF\textsubscript{50} and FEF\textsubscript{75} were used to analyze the expiratory loop and Zapletal reference values were used to calculate the predicted value of the FEV\textsubscript{1}\textsuperscript{16}.

**Oscillometric measurements**

Measurements using FOT (R.O.S., Oscilink®, Sensormedics®) were repeated 3 times with the nose clipped and with hands supporting the cheeks and mouth floor. FOT measurements were repeated before exercise and at 5, 14, and 24 minutes after exercise. We calculated the FOT values using 3 measurements. The measurements were performed before flow-volume loops and at least two minutes after previous flow volume loops to ensure a sufficient interval after forced breathing and to minimize the bronchodilating effect of a deep inspiration\textsuperscript{5,6}. 

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The characteristics most widely used to analyze FOT measurements are the lower frequency resistance and reactance and the resonance frequency. Since \( R_{rs} \) is, per definition, extrapolated, we used the resistance at 6 Hertz \( (R_{rs}) \). We found that in some children the resonance frequency exceeded the measuring range of the device (4-32 Hz); therefore we chose a derivative of this measurement in the reactance at 6 Hz \( (X_{rs}) \).

**Statistical analysis**

Best values of spirometric measurements and mean values of FOT measurements were used for statistical calculations. Results are expressed as mean values ± standard deviation (SD) for normally distributed data, as median (range) for non-parametric data or as numbers with corresponding percentages if nominal or ordinal. Comparison between values after administration of fluticasone propionate and placebo were performed after testing for Normality using a Shapiro-Wilk test. A paired samples t-test was used for normally distributed data and a Wilcoxon signed Rank test for not Normally distributed data. Correlations were calculated using Pearson or Spearman correlations as appropriate. In this cross-over design the SD of the difference in FEV\(_1\) between FP and placebo was set at 4.5%. With a power of 90% the detectable difference would have been 4.6%\(^1\). The level of significance was set at 0.05 with 95% confidence intervals (CI). Statistical calculations were made using SPSS® version 15.0 for Windows®, power calculation were made using PS: Power and Sample Size calculation version 3.0 for Windows.

**RESULTS**

Fifteen patients were selected and performed both tests. One patient did not meet the criteria of EIB, and two patients did not adhere to the protocol (strenuous activity prior to exercise provocation). This resulted in twelve children who finished the complete study protocol. Baseline measurements were comparable on both test days, and mean values of baseline spirometric, FOT, and patient characteristics are shown in table 1. In 6 out of 116 measurements (5%), the mean FOT value was calculated using only 2 instead of 3 acceptable measurements.

After placebo, exercise induced a fall in all spirometric indices. The time course of the fall of the FEV\(_1\), the FEV\(_1\)/FVC ratio and the FEF\(_{25}\), FEF\(_{50}\) and FEF\(_{75}\) can be found in figures 1a, 1b, 1c, 1d and 1e respectively. As can be seen in figures 1a, 1c and 1d the fall in FEV\(_1\) and FEF\(_{50}\) peaked 3 minutes after exercise and showed a subsequent partial recovery. The fall in the FEV\(_1\)/FVC ratio and FEF\(_{75}\) showed a later peak fall (12 minutes after exercise). FP significantly reduced the fall in FEV\(_1\) at 3, 6, 9, 12, 15 and 25 minutes after exercise; the FEV\(_1\)/FVC ratio was similarly affected. The fall in FEF\(_{50}\) however showed a significant difference between FP and placebo only 3, 6 and 9 minutes after exercise. FP significantly reduced the peak fall in FEV\(_1\).
Table 1, Patient characteristics and lung function values before both exercise provocation challenges.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>14.0 ± 1.1</td>
</tr>
<tr>
<td>Male gender (% of total)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 9</td>
</tr>
<tr>
<td>Allergy (% of total)</td>
<td>11 (92)</td>
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<tr>
<th></th>
<th>FP</th>
<th>Placebo</th>
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<tr>
<td>FEV1 (% of pred)</td>
<td>95.7 ± 10.8</td>
<td>92.0 ± 10.2</td>
</tr>
<tr>
<td>FEV1/FVC-ratio (%)</td>
<td>82.4 ± 8.2</td>
<td>79.8 ± 7.7</td>
</tr>
<tr>
<td>Xrs6 (kPa∙s∙l⁻¹)</td>
<td>−0.98 ± 0.68</td>
<td>−0.96 ± 0.72</td>
</tr>
<tr>
<td>Rrs6 (kPa∙s∙l⁻¹)</td>
<td>0.37 ± 0.12</td>
<td>0.36 ± 0.13</td>
</tr>
</tbody>
</table>

Figure 1, Time-course of change in A) FEV1, B) FEV1/FVC ratio C) FEF25 D) FEF50 and E) FEF75 after exercise in % of baseline with standard error from the mean. * indicate p<0.05 The dashed lines represent placebo and the solid lines represent Fluticasone propionate.
The effect of FP on the dynamics of EIAO after exercise, compared to placebo, respectively 19.3 ± 14.6% and 29.2 ± 14.8% (p=0.03, 95% CI: 0.9%-18.8%, power: 99.99%). After administration of FP, the peak fall in FEF_{25} and FEF_{50} were significantly smaller than after placebo: 28.6 ± 14.8% vs. 43.7 ± 20.4% (p=0.03, 95% CI: 1.4%-24.9%) and 32.5 ± 18.9% vs. 45.7 ± 13.6% (p=0.02, 95% CI: 3.2%-23.2%) respectively. The peak fall in FEV_{1}/FVC ratio and FEF_{75} were not significantly different after FP compared to placebo: 10.9 ± 7.9% vs. 16.0 ± 8.1% (p=0.12, 95% CI: −11.8-1.5%), and 38.3 ± 18.8% vs. 43.4 ± 13.2% (p=0.08, 95% CI: −10.3-20.6%) respectively.

After placebo, exercise induced a significant increase in Rrs_{6} and a significant decrease in Xrs_{6}. The change up to 24 minutes after exercise of the Rrs_{6} and Xrs_{6} can be found in figures 2a and 2b respectively. The increase in Rrs_{6} peaked 5 minutes after exercise and did not show a significant recovery 24 minutes after exercise. In contrast, the decrease in Xrs_{6} peaked 5 minutes after exercise and showed a continuous recovery thereafter. FP significantly affected the Rrs_{6} 24 minutes after exercise (p=0.02), while FP significantly affected the Xrs_{6} 5 minutes after exercise (p=0.02). FP significantly reduced the maximum increase of Rrs_{6} compared to the placebo, respectively 176.5 ± 59.1% and 201.0 ± 63.8% (p=0.05, 95% CI: 0.5-48.7%, power 99.5%). The maximum decrease in Xrs_{6} was not significantly different after FP compared to the placebo, 286.7 (105.6-769.7)% and 349.0 (100.0-1960.0)% respectively (p=0.06).

The correlation between pre-exercise spirometric and FOT measurements can be found in table 2.

### Table 2, The Spearman association between FOT and spirometry measurements before exercise

<table>
<thead>
<tr>
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<th>After FP</th>
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<tbody>
<tr>
<td></td>
<td>FEV₁</td>
<td>FEF₂₅</td>
<td>FEF₅₀</td>
<td>FEF₇₅</td>
</tr>
<tr>
<td>Rrs₆</td>
<td>−0.48</td>
<td>−0.62*</td>
<td>−0.75**</td>
<td>−0.70*</td>
</tr>
<tr>
<td>Xrs₆</td>
<td>−0.53</td>
<td>−0.46</td>
<td>−0.59*</td>
<td>−0.65*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>After Placebo</th>
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<tbody>
<tr>
<td></td>
<td>FEV₁</td>
<td>FEF₂₅</td>
<td>FEF₅₀</td>
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<tr>
<td>Xrs₆</td>
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<td>−0.27</td>
<td>−0.48</td>
</tr>
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* marks statistically significant difference with p<0.01
* marks statistically significant difference with p<0.05
Figure 2, Boxplots of A) resistance at 6 Hz and B) reactance at 6 Hz at 5, 14 and 24 minutes after exercise. Open circles represent outliers.
DISCUSSION

All spirometric measurements, as well as FOT measurements, changed significantly after exercise. The effect of FP on FEV₁ was significant 3 to 25 minutes after exercise, while the effect on FEF₅₀ was only significant over the first 9 minutes after exercise. The effect of FP peaked 5 minutes after exercise for Xrs₆ and 24 minutes after exercise for Rrs₆. These results suggest that the effect of FP on EIB was more marked in the conducting airways.

To our knowledge this is the first study to analyze the dynamics of the airway obstruction in EIB using both spirometry and FOT simultaneously in children with asthma. Hyperpnea during and immediately after exercise dehydrates the airway wall lining. The subsequent osmotic change of the airway wall lining causes the release of mediators through degranulation of mast cells. These mediators cause contraction of airway smooth muscle, microvascular leakage resulting in congestion of the airway mucosa, and mucus hypersecretion obstructing the airways. We observed a rapid fall in FEV₁, FEF₂₅, FEF₅₀ and Xrs₆ peaking immediately after exercise, that showed a steady recovery thereafter. We speculate that this recovery may be compatible with a reduction in airway tone, which may be caused by relaxation of airway smooth muscle.

The mean fall in the FEF₇₅, FEV₁/FVC ratio and the Rrs₆ had a different time course, showing a delayed and prolonged fall 15 minutes after exercise. The fall in FEV₁ we observed, accompanied by a smaller fall in FEV₁/FVC ratio, indicates a simultaneous fall in FVC, possibly suggesting airway closure. We speculate that the observed prolonged changes in the FEF₇₅, FEV₁/FVC ratio and the Rrs₆ are compatible with a decreased airway lumen, which may be largely caused by congestion of the airway wall and/or mucus.

The congestion of the airway wall and secretion of mucus take longer to build up than airway smooth muscle contraction, recede slower, and have less impact on the conducting airways, which may explain the observed discrepancy in dynamics of different spirometric and FOT measurements. Furthermore, the repetitive forced breathing maneuvers performed after exercise might have enhanced the recovery of the patency of the conducting airways which we observed as several studies have shown that deep inspiration primarily bronchodilates the conducting airways.

Tvagelkos et al. studied adult asthmatic patients using low frequency FOT measurements and PET scanning and stated that a bronchoprovocation led to a simultaneous constriction of small and large airways, but not just large airways alone. Campana et al. made a similar analysis and also stated that both the larger and smaller airways contribute to airway obstruction after bronchoprovocation with metacholine in adult asthmatics.

Most of the studies measuring resistance, reactance, and spirometry were performed in adult asthmatics. We realize that measurements of spirometry and FOT in children indeed represent different lung mechanical properties than measurements of these parameters in adults as lung physiology changes during growth. The discrepancy of the dynamics of the
change in $R_{rs6}$ and $X_{rs6}$ are of interest. The prolonged increase in $R_{rs6}$ compared to the decrease in $X_{rs6}$ may be caused by a sustained obstruction of the smallest conducting airways, in line with the prolonged fall in $FEF_{75}$. However, the observed discrepancy between $R_{rs6}$ and $X_{rs6}$ may be also due to the recovery of inhomogeneous ventilation and/or a shunting effect of bronchial wall compliance immediately after exercise.

The effect of a single dose of inhaled steroids on bronchial hyperresponsiveness to indirect challenges has been well documented and confirmed in our study with both FOT and spirometry. We hypothesize that this effect was due to a direct non-genomic effect of the inhaled FP on inflammatory cells, inhibiting the release of mediators. A direct effect of a single high dose of corticosteroid on inflammatory cells has been found previously in vitro and in vivo. Llewellyn-Jones et al. analyzed the direct in vitro effect of FP on inflammatory markers and found that FP decreases the release of these markers. More recently, Zhou et al. analyzed the effect of budesonide on mast cell stability through the IgE mediated release of Histamine and Ca$^{2+}$. They found a stabilizing effect after a single high dose of budesonide in guinea pigs. Kippelen et al. found that a single high dose of beclomethasone significantly reduced the airway obstruction and the excretion of urinary mediators in response to eucapnic voluntary hyperventilation in asthmatic adults and elite athletes, hypothesizing that beclomethasone blunted mast cell activation. The impact of the effect of FP on EIB in our study seemed to be greater in the conducting airways. This could be due to the relatively large particle size of fluticasone mainly depositing in the conducting airways. Particle size is of importance for penetration of the aerosol as well as the effect of the medication. Therefore it would be of interest to study the effect of a small particle inhaled corticosteroid on EIB.

Several remarks can be made about our study. Interpretation of FOT measurements is difficult and still controversial, as different parameters have been linked with several pathophysiological changes. There is evidence however that changes in $R_{rs6}$ and $X_{rs6}$ can be linked to changes in the smaller airways.

As FOT measurements require regular calm breathing, measurements in the first few minutes after exercise are not technically feasible. We measured FOT 5 minutes after exercise as EIB as measured with the FEV$_1$ peaks between 3 to 6 minutes after exercise. A pressurized head gear reduces upper airway shunt and would yield the best result. In light of the strenuous exercise and the cumbersome nature of such devices we chose not to use this device. Therefore, the FOT measurements suffered from an expected upper airway shunt as observed in previous studies. The upper airways shunt causes energy from the oscillating air to be absorbed by the relative high compliant upper airways (cheeks and the base of the mouth). These studies used the same data set and concerned children up to 9 and 13 years of age, respectively, while our study population concerns older children with a mean age of 14.0 years. Furthermore, the upper airway shunt has the biggest impact on higher frequencies; therefore we only analyzed lower frequency measurements. FP did not reduce the decrease in $X_{rs6}$
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significantly (p=0.06). However, the measurements of the Xrs6 showed a large spread which, together with the relative small sample size, probably affected the statistical significance.

Deep inspiration can have a bronchodilating effect which is especially strong after exercise6. The time period of 2 minutes between forced breathing maneuvers and FOT measurements as we used, as advised by the current ERS recommendations5, may have been too short to completely negate the effect of deep inspiration.

One individual showed a substantially greater fall in FEV1 after FP. A large drop in FEV1 and the perceived dyspnea caused the patient to request a bronchodilator shortly after exercise on both occasions. This was probably before the peak fall in FEV1, making accurate analysis of both FOT and spirometric data of this individual impossible.

In conclusion, repetitive spirometric and FOT measurements after exercise show a rapid narrowing and steady recovery of the patency of the conducting airways, and indicate a delayed and prolonged recovery of the smaller airways. A single high dose of inhaled FP reduces EIB and seems to employ its effect mainly in the conducting airways.
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