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

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Chapter 6

Association of the asthma control questionnaire with exercise induced bronchoconstriction

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ABSTRACT

Introduction
Asthma is a common chronic disease in childhood and featured by bronchial hyperresponsiveness to exercise (EIB). In daily clinical practice the report of EIB is used to assess the level of control of asthma. The asthma control questionnaire (ACQ) is a tool to evaluate control of asthma in children. The aim of this study was to evaluate the relationship between the ACQ and EIB.

Methods
Two hundred children aged 12.5 ± 2.5 years with a pediatrician diagnosed mild to moderate asthma filled out an ACQ and performed an exercise provocation test in cold air. EIB was defined as a fall in FEV₁ of 15%.

Results
86 Of the 200 children had a positive exercise challenge. There was no relationship between the categorical ACQ and the occurrence of EIB (p=0.39). There was no difference in the occurrence of EIB between genders (p=0.12). The positive predictive value of the ACQ for EIB was 51% and the negative predictive value for EIB was 59%. In comparison to girls the male gender carried an odds ratio (OR) of 0.48 for having an indifferent control of asthma (p=0.04; CI: 0.23-0.96), and an OR of 0.46 for having a not well controlled asthma (p=0.03; CI: 0.23-0.93).

Conclusion
This study shows that the ACQ is not related to EIB in children with asthma. Remarkable is the percentage (41%) of children that, despite well controlled asthma according to the ACQ, had EIB, which implies a not well controlled asthma. Boys were more likely to report well controlled asthma, although boys and girls were equally likely to have EIB.
INTRODUCTION

Asthma is a common chronic disease in childhood characterized by episodic airway narrowing. Exercise frequently causes airway narrowing in asthmatic children and bronchial hyperResponsiveness to exercise (EIB) is highly specific for asthma. Bronchial hyperreactivity can be assessed with indirect tests such as exercise or direct challenge tests such as metacholine. Direct triggers induce airway narrowing through direct stimulation of the effector cells, such as airway smooth muscle. Indirect triggers stimulate inflammatory cells, resident in the asthmatic airway wall, to release mediators, inducing airway narrowing. EIB may have a detrimental effect on the quality of life and the majority of asthmatic children consider EIB to be the worst aspect of their asthma. In daily clinical practice the report of EIB is used to assess the level of control of asthma and may alter the therapeutic regimen. However, self-reported exercise induced symptoms do not correlate well with the occurrence of EIB.

The asthma control questionnaire (ACQ) is a widespread used tool to evaluate control of asthma in clinical trials, clinical practice and surveys in children. In the recent update of the global initiative for asthma guidelines (GINA), the ACQ is recommended as a tool to measure asthma control. We hypothesized that the ACQ could be used as a predictor of EIB. The aim of this study was to evaluate the relationship between the ACQ and EIB.

MATERIALS AND METHODS

From the outpatient clinic of the pediatric department of the Medisch Spectrum Twente, 200 children, aged 12.5 ± 2.5 years, with a pediatrician diagnosed mild to moderate asthma performed an exercise provocation test. Immediately prior to the exercise provocation test, all children filled out the ACQ. Children performed an exercise provocation test between February 2005 and March 2010. The majority of the children used inhaled corticosteroids (ICS), 108/200 (54%) received ICS in combination with long acting beta-agonists (LABA) and 50/200 (25%) children received ICS monotherapy. Leukotriene receptor antagonists (LTRA) were used by 40/200 (20%) children, the majority in combination with ICS 39/40 (98%). 41 Patients only used short acting beta agonists as required. Subjects were required to withhold the use of long acting or short acting bronchodilators for 24 hours before testing. No vigorous exercise was permitted for 4 hours prior to the exercise provocation test.

Exercise testing was performed on a treadmill (Ti22 Horizon Fitness®, Cottage Grove, WI, USA) according to ATS/ERS recommendations. Baseline spirometry was performed and the prechallenge FEV₁ was documented as the best FEV₁ of three comparable measurements. Exercise challenges were performed in the local skating rink, to obtain cold and dry air (2-5°C, 1-5 mg∙l⁻¹ H₂O). 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 predicted maximum (210-age) after an acclimatization period of 2 minutes. Heart rate was monitored with a Polar Sport tester (Polar®, Kempele, Finland).

A Masterscope® (Jaeger®, Hoechberg, Germany) was used to measure spirometry. Flow-volume loops were recorded using standard ERS protocol. 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 FEV₁ were used to analyze the expiratory loop and Zapletal reference values were used to calculate the predicted values. A fall of more than 15% of FEV₁ was considered positive for EIB.

The 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 immediately 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.

Results were expressed as mean values ± standard deviation (SD) for normally distributed data, as median (range) 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)).

First, the crude association between ACQ and EIB was analyzed by univariate logistic regression. After this, unpaired t-tests, Mann-Whitney U or Chi-square tests, as appropriate, were performed to identify a subset of independent variables that were associated with ACQ. The a priori list of potential confounding variables is displayed in Table 1. Only those variables

<table>
<thead>
<tr>
<th>Table 1, patients' characteristics, outcome of the exercise provocation challenge and spirometric values before exercise by outcome of the ACQ. Data were expressed as numbers (% of group), mean ± standard deviation or median (range).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-controlled</td>
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<tr>
<td>-----------------</td>
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<tr>
<td>ACQ &lt; 0.75</td>
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<tr>
<td><strong>n = 98</strong></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>12.7 ± 2.4</td>
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<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>71 (72)</td>
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<tr>
<td>BMI</td>
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<tr>
<td>19.1 ± 2.9</td>
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<tr>
<td>FEV₁, (% predicted)</td>
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<tr>
<td>94.7 ± 15.3</td>
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<tr>
<td>ICS monotherapy (%)</td>
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<tr>
<td>29 (30)</td>
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<tr>
<td>ICS+LABA (%)</td>
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<tr>
<td>49 (50)</td>
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<tr>
<td>LTRA (%)</td>
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<tr>
<td>13 (13)</td>
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<tr>
<td>EIB (%)</td>
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<tr>
<td>40 (41)</td>
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<tr>
<td>Fall in FEV₁, after exercise (range)</td>
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<tr>
<td>17.2 (−1.8;64.2)</td>
</tr>
</tbody>
</table>

* p < 0.05 when compared to indifferent control and well-controlled groups. 
ACQ and EIAO in children

associated with the ACQ with a significance at or below \( p=0.15 \) were tested for an association with EIB. Variables also associated with EIB with a significance at or below \( p=0.15 \) were considered as potential confounders in the relationship between ACQ and EIB and were entered into multivariate logistic regression analysis. Correlations were calculated using Pearson or Spearman correlations as appropriate.

Receiver operating characteristics analyses were performed using a drop in FEV\(_1\) of more than 15\% as spirometric cut-off, missing values were excluded from analysis. SPSS® for Windows® version 15 (IBM, Chicago, IL, USA) was used to perform all analysis.

RESULTS

Two hundred children performed an exercise challenge test in cold air. When setting the threshold for exercise induced bronchoconstriction at a fall in FEV\(_1\) of 15\%, 86 of the 200 children had a positive exercise challenge. Of the girls, 27/73 (37\%) showed EIB, compared to 59/127 (47\%) of the boys (\( p=0.12 \)).

When dividing children into 3 groups according to asthma control as suggested by Juniper et al.\(^{11}\), 98 children showed well controlled asthma (ACQ <0.75), 49 children showed an indifferent control of their asthma (ACQ 0.75-1.49) and 53 children showed uncontrolled asthma (ACQ 1.50). Characteristics of these groups can be seen in table 1.

There was no correlation between the categorical ACQ and the occurrence of EIB (\( p=0.39 \)) or between question 3 of the ACQ (exercise limitation) and the occurrence of EIB (\( p=0.73 \)). The correlation between the overall ACQ and fall in FEV\(_1\) after exercise was −0.12 (\( p=0.09 \)). Fall in FEV\(_1\) after exercise is plotted against categorical ACQ in figure 1.

Using the receiver operating characteristics (ROC) curve for uncontrolled asthma, defined as an ACQ ≥ 1.50, we found an area under the curve (AUC) for fall in FEV\(_1\) after exercise of 0.58 (\( p=0.07 \); CI: 0.49-0.68), see figure 2.

Of the list of potential confounders found in table 1, only gender was related with the categorical ACQ (\( p=0.04 \)). In the univariate model, when compared to well controlled asthma, the male gender carried an odds ratio (OR) of 0.48 for having an indifferent control of asthma (\( p=0.04 \); CI: 0.23-0.96), and an OR of 0.46 for having a not well controlled asthma (\( p=0.03 \); CI: 0.23-0.93).

In the multivariate model, the gender corrected relationship between the categorical ACQ and EIB was still not significant. In this model the ACQ carried an OR of 1.26 for EIB (\( p=0.19 \); CI: 0.89-1.77) and male gender carried an OR of 1.59 for EIB (\( p=0.13 \); CI: 0.87-2.90).
Figure 1. Fall in FEV₁ after exercise plotted against asthma control.

FEV₁: Forced expiratory volume in the first second. EIB: Exercise Induced Bronchoconstriction.

Figure 2. Receiver operating characteristic curve of fall in FEV₁ after exercise in differentiating asthma control as measured with the ACQ (ACQ ≥ 1.50 vs. ACQ < 1.50). The area under the curve for fall in FEV₁ after exercise was 0.58 (p=0.07; CI: 0.49-0.68).
DISCUSSION

This study shows that the ACQ is not related to the occurrence of EIB in children with asthma. Most striking is the percentage (41%) of children that, despite well controlled asthma according to the ACQ, had bronchial hyperresponsiveness to exercise, implicating a not well controlled asthma. Boys were more likely to report well controlled asthma, with boys and girls equally likely to have EIB.

To our knowledge this is the first study to investigate asthma control in children as measured with the ACQ and the occurrence and severity of EIB. In our study, the predictive value of the ACQ for the occurrence of EIB was limited. When using the cut-off points from Juniper et al. we found that the positive predictive value of the ACQ was 51% while the negative predictive value of the ACQ was 59%\textsuperscript{11}. 41% Of the children with well controlled asthma, regardless of medication regimen, showed EIB, some of which were severe. Hagmolen of ten Have et al. found that 18% of children with well controlled asthma had a moderate to severe bronchial hyperresponsiveness to metacholine\textsuperscript{17}. They used a standard questionnaire for assessing control of asthma in children treated by general practitioners. The high percentage of children that had bronchial hyperresponsiveness to exercise in our study could be due to the severity of asthma as we studied hospital-based children treated by a pediatrician. Rupp et al. screened high-school children with both a questionnaire and an exercise provocation test and found an overall prevalence of EIB of 12%\textsuperscript{18}. Of the children showing EIB, 64% (14 of 22) did not have deviant questionnaires. Weinberger et al. studied asthmatic children in a tertiary referral centre and found similar results\textsuperscript{19}. In asthmatic adults Quaedvlieg et al. analyzed the association between asthma control measured with the ACQ and metacholine induced bronchial hyperresponsiveness\textsuperscript{19}. They found that a provocative concentration of 3.4 mg·ml\textsuperscript{-1} metacholine differentiated uncontrolled asthma from controlled and indifferent controlled asthma with a sensitivity and specificity of 70% (AUC 0.72; \textit{p}<0.01). We found that the fall in FEV\textsubscript{1} after exercise could not make that differentiation (AUC 0.58; \textit{p}=0.07). Apparently children are less capable of self assessment of asthma control as measured with the ACQ. In a recent review, Randolph states this is also true for adolescent athletes\textsuperscript{9}. Aaron et al. studied a large cohort of physician diagnosed asthmatic adults using metacholine provocation challenges and found that 29-32% did not have asthma\textsuperscript{21}. The main difference between this study and ours is that we analyzed (asthmatic) children with an indirect challenge test which is more specific than a direct challenge test such as metacholine to assess asthmatic airway inflammation\textsuperscript{4}.

The positive predictive value of the ACQ for bronchial hyperresponsiveness was poor (51%), and there was no relationship between question 3 (exercise limitation) and EIB. Abu-Hassan et al. and Seear et al. observed that self-reported exercise induced symptoms are in the minority of cases caused by EIB\textsuperscript{7,8}. The exercise related question in the ACQ seems to be
no exception to that find. Boys and girls were equally likely to have EIB, but boys reported well controlled asthma on the ACQ significantly more than girls and had an OR of between 0.46-0.48 to have well controlled asthma. This was also observed in the study by van Dellen et al. who analyzed the ACQ in a multi-ethnic group in Amsterdam and found that the male gender carried an OR of 0.5 for well controlled asthma\textsuperscript{12}.

Several remarks can be made about this study. The ACQ is mainly developed as a tool to longitudinally evaluate control of asthma in a research set-up. In this study the ACQ was used as a device to evaluate asthma control cross-sectionally in comparison with another modality of asthma control, i.e. EIB. Defining EIB with a drop in FEV\textsubscript{1} of more than 15% is generally accepted in the clinical setting, however, 10% can also be used in a research setting\textsuperscript{13}. Choosing the less stringent cut-off of 10% would reduce the negative predictive value of the ACQ for EIB even further (Data not shown). Treating asthma relies on two modalities, disease control and disease severity, in the GINA guideline disease control has been advocated as the mainstay of treatment. Discerning control from severity can be difficult in asthma\textsuperscript{22} but the occurrence of EIB rather than the depth of the fall in FEV\textsubscript{1} after exercise can be seen as a poor control of asthma\textsuperscript{1,3}. In this study we found no relationship between the ACQ and the occurrence or the severity of EIB.

In conclusion, the ACQ does not provide conclusive information about the level of control regarding the occurrence and severity of EIB. This indicates that both tools should be used and are not interchangeable. Pediatricians should regard the ACQ as a tool which provides complementary information about the control of asthma in children, rather than a defining tool for assessing the control of asthma in daily practice. Individual clinical decisions based on the outcome of the ACQ should be made with caution.
REFERENCES

Chapter 6

