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

Driessen, J.M.M.

Publication date
2013

Chapter 7

Prediction of the occurrence of exercise induced bronchoconstriction in asthmatic children

Submitted

Jean Driessen, Marjolein Brusse-Keizer, Hans Nieland, Wim van Aalderen, Boony Thio, Frans de Jongh

ABSTRACT

Rationale

Exercise induced bronchoconstriction (EIB) is a transient airway obstruction following exercise and is diagnosed with an exercise provocation challenge. In children bronchial hyperresponsiveness has been related to body mass index (BMI) and pre-exercise lung function. The aim of the study was to identify independent predictors for EIB in children with mild to moderate asthma using anthropometric, spirometric and forced oscillation technique measurements.

Methods

Allergic asthmatic children performed an exercise challenge in cold air. Pre-exercise anthropometric, spirometric and FOT measurements were collected. After exercise spirometric and FOT measurements were collected up till 30 minutes after exercise. EIB was defined as a fall in FEV_1 of more than 15%.

Results

59 children (age 13.4 ± 2.3 years) completed the protocol. In a multivariate logistic regression analysis we found that age and gender corrected BMI z-scores and MEF_{50} (% of pred) before exercise predicted the occurrence of EIB best, with respectively odds ratios of 2.7 ($p<0.01$; CI:1.4-5.1) and 0.96 ($p=0.02$; CI: 0.93-0.99). There was no correlation between pre-exercise FEV_1 or FOT measurements and EIB, although the pre-exercise resonance frequency of the FOT showed a trend towards a lower resonance frequency in children without EIB ($p=0.10$).

Conclusions

Our study shows that the BMI z-score and the pre-exercise MEF_{50} are independent predictors of EIB in asthmatic children.

INTRODUCTION

Exercise induced bronchoconstriction (EIB) is defined as a transient airway obstruction following exercise and is highly specific for asthma[1]. EIB is classically diagnosed with a fall in FEV_1 of more than 15% after an exercise challenge[2]. A normal spirometry before exercise cannot predict the occurrence of EIB. However, an obstructive pre-exercise flow volume curve, on visual inspection, has been associated with the occurrence of EIB[3]. Repetitive forced breathing, as required by spirometry can influence bronchial tone. The forced oscillation technique (FOT) is a sensitive effort independent lung function measurement technique which does not require repetitive forced breathing and can asses airway resistance and reactance[4]. The lower frequency resistance reflects the patency of the conducting airways[4]. The lower frequency reactance reflects the capacitive properties of the respiratory system i.e. lung stiffness, intraparenchymal airway mechanics and airway-parenchyma interdependence[5]. Therefore, FOT measurements may be able to predict the occurrence of EIB.

A high body mass index (BMI) has been associated with the report of exercise induced cough, wheeze and bronchial hyperresponsiveness to metacholine in asthmatic children[6]. Children previously not diagnosed with asthma, that were obese had an increased risk for EIB[7], while children with a relatively low BMI had a reduced risk for EIB[8]. We hypothesize that BMI is a predictor of the occurrence of EIB in asthmatic children.

The aim of the study was to identify independent predictors for EIB in children with mild to moderate asthma using anthropometric, spirometric and FOT measurements.

MATERIALS AND METHODS

Study design

The study had a cross-sectional, observational design. All children performed an exercise challenge. Before and after exercise, lung function was measured using FOT and flow-volume loops. EIB was defined as a fall in FEV_1 of more than 15%[2]. Thirty minutes after the exercise challenge, or earlier on a patient's request, 400 µg Salbutamol pressurized meterdose inhaler was given in conjunction with a spacer device. Fifteen minutes after inhalation of salbutamol, measurements were repeated to ensure that lung function had returned to pre-exercise level.

Subjects

Children (range 8-17 years) with a mild to moderate asthma from the pediatric outpatient clinic of Medisch Spectrum Twente were selected, with 73% of the children having an allergy as defined by a positive radioallergosorbant test. BMI was corrected for age and gender and calculated as standard deviation score (z-score)[9]. One unit in BMI-z-score represents 1 SD from the mean. Criteria from Cole et al. were used to determine if children were overweight or obese[9]. Children were asked to withhold the use of long acting bronchodilators for 24 hours and the use of short acting bronchodilators for 8 hours before the tests. No vigorous exercise was permitted for 4 hours before the exercise challenge.

Exercise challenge

Exercise challenges were performed in the local skating rink, to obtain standardized cold, dry air conditions (2-5°C, 1-5mg·l^{-1} H_2O). Exercise challenges were performed on a treadmill (Ti22 Horizon Fitness®, Cottage Grove, WI, USA) with a 10 degree slope, on which children ran for a 4 minute period with a heart rate at 90 percent of predicted maximum (210-age). This was preceded by a run in period of 2 minutes[2,10]. The nose was clipped to accommodate equal testing circumstances for all children. Heart rate was monitored with a Polar Sport tester (Polar®, Kempele, Finland).

Spirometric measurements

A Masterscope® (Jaeger®, Hoechberg, Germany) was used to measure spirometry. Flow-volume loops were recorded using the standard ERS protocol[11]. Before exercise, flow volume loops were duplicated. After exercise flow volume loop measurements were collected in duplex at 1, 3, 6, 9, 12, 15, 20, 25 and 30 minutes. The best values for the forced vital capacity (FVC), the forced expiratory volume in the first second (FEV_1) and mid expiratory flow (MEF_{50}) were used to analyze the expiratory loop and Zapletal reference values were used to calculate the predicted values[12].

Oscillometric measurements

FOT measurements were performed before flow-volume loops and at least 2 minutes after previous flow volume loops to ensure a sufficient interval after forced breathing[4]. Measurements using FOT (IOS, Jaeger®, Hoechberg, Germany) were performed for 30 seconds with nose clipped and with hands supporting cheeks and mouth floor. After exercise FOT measurements were performed at 5, 14 and 24 minutes. We analyzed low frequency resistance (Rrs_5) and reactance (Xrs_5) as well as the resonance frequency (Fn).

Statistical analysis

Best values of spirometric measurements and full time analysis of FOT measurements were used for statistical calculations. Results were 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. The level of significance was set at 0.05 (95% confidence intervals (CI)). To identify a subset of variables (Gender, BMI z-score, FEV_1, MEF_{50}, FEV_1/FVC ratio, Rrs_5, Xrs_5 and Fn) that were associated with EIB, 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. Variables that were associated with EIB with a significance at or below p=0.15 were considered candidate variables for multivariate logistic regression analysis and were all entered. Subsequently, variables with the highest p-value were eliminated step by step until the fit of the model decreased significantly (based on likelihood-ratio tests). Receiver operating characteristics analyses were performed using a fall in FEV_1 of more than 15% as spirometric cut-off. SPSS® for Windows® version 15 (IBM, Chicago, IL, USA) was used to perform all analyses.

RESULTS

Sixty-one children (age 13.4 ± 2.3 years) with a history of mild-moderate asthma performed an exercise challenge in cold air. A vital capacity of less than 80% of predicted before exercise was regarded as a possible sign of a restricted lung function and these patients were excluded from the study (2 children). In total 59 children completed the protocol. When setting the threshold for exercise induced bronchoconstriction at a drop in FEV_1 of 15%, 28 of the 59 children showed EIB.

Characteristics for each group are shown in table 1. Twelve children (20.3%) were overweight, of which 2 (3.4%) were obese (chi-square p=0.12; OR 2.70; CI: 0.71-10.23; p=0.14). The FEV_1 dropped 29.9 ± 13.9% for children with EIB and 8.4 ± 3.8% for children without EIB, while the MEF_{50} dropped 43.0 ± 14.6% for children with EIB and 14.4 ± 8.5% for children without EIB.

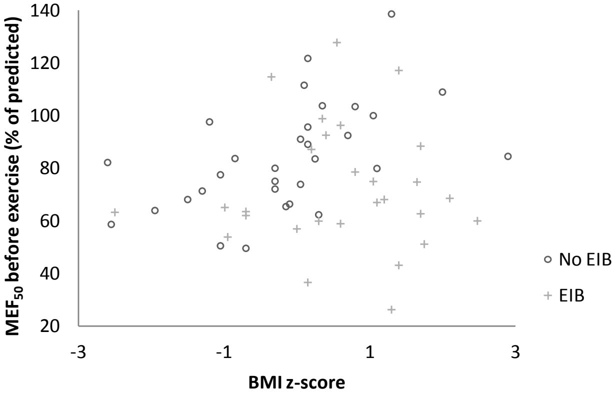
Using a multivariate logistic regression model for baseline characteristics (Gender, BMI z-score, FEV_1, MEF_{50}, FEV_1/FVC ratio, Rrs_5, Xrs_5 and Fn) and outcome of the exercise challenge we found that BMI z-score and MEF_{50} (% of predicted) before exercise were the best independent predictors of occurrence of EIB. An increase in BMI z-score of 1 SD leads to an 2.7-fold

Table 1, patients' characteristics and spirometric values before exercise. Data were expressed as numbers (%) or mean ± standard deviation.

	EIB n=28	no-EIB n=31	p-value	95% CI
Male (%)	20 (71%)	20 (65%)	0.39	
Age (years)	13.2 ± 2.1	13.6 ± 2.5	0.37	–0.8 - 1.6
Length (cm)	159.0 ± 15.4	159.7 ± 13.7	0.85	–6.8 - 8.3
BMI z-score	0.59 ± 1.11	–0.14 ± 1.20	0.02	0.13 - 1.34
Overweight (%)	8 (29)	4 (13)	0.12	
FEV_1 (% predicted)	101.6 ± 16.7	105.6 ± 14.7	0.33	–4.2 - 12.2
MEF_{50} (% predicted)	72.0 ± 23.8	83.9 ± 20.5	0.04	0.3 - 23.4
FEV_1/FVC-ratio	79.3 ± 10.0	84.2 ± 6.5	0.03	0.5 - 9.2

EIB: Exercise Induced Bronchoconstriction; CI: Confidence Interval; BMI z-score: age and gender corrected body mass index; FEV_1: Forced Expiratory Volume in the first second; MEF_{50}: Mid Expiratory Flow; FEV_1/FVC-ratio: Forced Expiratory Volume in the first second as percentage of the Forced Vital Capacity.

Figure 1, BMI z-score plotted against pre-exercise MEF_{50} (% of predicted) for children with and without EIB. There was no relation between BMI z-score and pre-exercise MEF_{50} (p=0.23).



increased risk of experiencing EIB (OR: 2.7; 95% CI:1.4-5.1; p<0.01) while an increase in MEF_{50} (% of predicted) before exercise of 1% leads to a reduced risk of experiencing EIB of 4.2% (OR: 1.04; 95% CI: 1.01-1.08;p=0.02), implicating that an increase in MEF_{50} of predicted of 10% leads to a 42% decrease in the likelihood to experience EIB. We did not find an association between pre exercise MEF_{50} and BMI z-score (OR: 2.1; 95% CI: −1.4 - 5.5; p=0.23) as can be seen in figure 1.

After exercise, 4 Fn measurements exceeded the measurement range of the device (3-35 Hz) and were therefore excluded from the analysis. In these patients the median increase in Fn was 19.9 Hz with a range from 5.2 to 28.8 Hz while the median fall in FEV_1 was 43.1% with a range from 7 to 64%. Values of FOT measurements before and change after exercise can be seen in table 2. We did not find a correlation between FOT measurements and BMI or EIB.

We used receiver operating characteristics (ROC) of change in low frequency FOT measurements to differentiate children with EIB from children without EIB. ROC-curves can be seen in figure 2.

Table 2, FOT measurements before and change after exercise. Data was expressed as median (range).

	EIB	no-EIB	
Before exercise	n=28	n=31	p-value
Rrs_5 ($kPa{\cdot}s{\cdot}l^{-1}$)	0.45 (0.26;0.92)	0.43 (0.24;0.84)	0.26
Xrs_5 ($kPa{\cdot}s{\cdot}l^{-1}$)	−0.14 (−0.48;−0.05)	−0.13 (−0.35;−0.05)	0.20
Fn (Hz)	17.8 (8.6;28.0)	13.6 (8.4;33.7)	0.10
Change after exercise			
Rrs_5 ($kPa{\cdot}s{\cdot}l^{-1}$)	0.27 (−0.06;0.76)	0.10 (−0.06;0.57)	<0.01
Xrs_5 ($kPa{\cdot}s{\cdot}l^{-1}$)	−0.17 (−0.74;−0.50)	−0.04 (−0.65;0.13)	<0.01
Fn (Hz)	7.3 (−8.7;20.0)	3.6 (−2.3;14.8)	0.10

EIB: Exercise Induced Bronchoconstriction; Rrs_5: Resistance at 5 Hertz; Xrs_5: Reactance at 5 Hertz; Fn: Resonance frequency.

Figure 2, ROC curves for change in low frequency FOT measurements and resonance frequency using exercise induced bronchoconstriction as defined by a fall in FEV_1 of more than 15% as the golden standard.

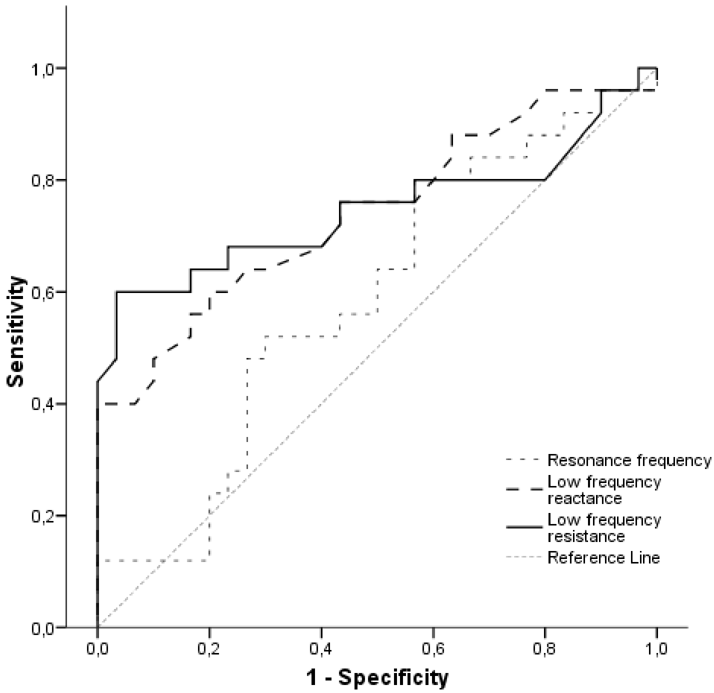


Table 3, change in low frequency measurements and their specificity and sensitivity when compared with a fall in FEV_1 of 15%.

	Cut-off	Sensitivity	Specificity
Rrs_5 ($kPa \cdot s \cdot l^{-1}$; %)	0.16; 33	71%	74%
Xrs_5 ($kPa \cdot s \cdot l^{-1}$; %)	–0.07; 38	68%	71%

Rrs_5: Resistance at 5 Hertz; Xrs_5: Reactance at 5 Hertz.

For Rrs_5 the area under the curve (AUC) was 0.75 (p<0.01; CI: 0.62-0.89) and for Xrs_5 the AUC was also 0.75 (p<0.01; CI: 0.62-0.88). The change in Fn was not able to differentiate children with EIB from children without EIB with an AUC of 0.59 (p=0.27; CI: 0.43-0.74) Threshold parameters can be found in table 3.

DISCUSSION

Our study shows that the BMI z-score and the pre-exercise MEF_{50} are independent predictors of EIB in asthmatic children. Pre-exercise FOT and FEV_1 measurements were not related to the occurrence of EIB, although the pre-exercise resonance frequency of the FOT showed a trend towards a lower resonance frequency in children without EIB in univariate analysis (p=0.10).

To our knowledge this is the first study that investigates the predictive value of anthropometric, spirometric and FOT measurements for EIB in children with mild to moderate asthma. The association between BMI and EIB we observed was found in children with a BMI z-score that ranged from low (−2.6) to high (+2.9). Tantisira et al. found an association in asthmatic children between BMI and bronchial hyperresponsiveness to metacholine, although the pre-challenge FEV_1 was a confounder[6]. Calvert et al. analyzed a large group of children with a relatively low weight (average BMI z-score lower than 0), who were not previously diagnosed with asthma, and found that children with EIB had higher BMI z-scores than children without EIB[8]. The causality of the relation between BMI and the occurrence of EIB in non obese children, as observed in our study and in the study of Calvert et al. is subject of debate.

Since there is evidence that the BMI is related to the development of asthma in both children and adults, direct causality has been proposed as the main contributor of the relationship between BMI and EIB[13-16]. The observations that leaner asthmatic children have a smaller chance for the occurrence of EIB strengthens this hypothesis.

A reluctance to participate in physical exercise in children with EIB, leading to a more sedentary lifestyle and obesity, may also explain the association between BMI and EIB (reverse causality)[17,18]. However we studied asthmatic children with an average weight, making it unlikely that reverse causality is the main contributor of the relationship between BMI and the occurrence of EIB.

Obesity influences EIB on a lung mechanical level. Exercise induced deep inspiration leads to mechanical stretch of smooth muscle in the airway wall, reducing smooth muscle tone, which can reduce bronchoconstriction[19]. Obesity may limit this stretch and consequently enhance EIB, Boulet et al. showed that obese adults avoid deep inspiration in metacholine challenges[20]. However as there were only 2 obese children in our study group it is unlikely that a mechanical phenomenon contributed substantially to the observed relation between BMI and the occurrence of EIB.

We found that a low pre-exercise MEF_{50}, but not a low pre-exercise FEV_1, was associated with the occurrence of EIB. Linna analyzed pre-exercise flow volume loops and found that an obstructive expiratory loop on visual assessment predicted the occurrence of EIB[3]. This is in line with our observation as MEF_{50} can be regarded as an index of an obstructive flow volume loop[21]. The pre-exercise FOT measurements did not predict for the occurrence of EIB, although a trend could be seen in resonance frequency (p=0.10). The large spread of the resonance frequency could be the reason why the difference was not statistically significant.

Lower frequency resistance measurements can be used to analyze EIB. We found an increase in the Rrs_5 of 33% and a decrease in the Xrs_5 of 38% corresponded with a fall in FEV_1 of 15%. This is in line with Malmberg et al. who found that in preschool children an increase of 35% of the Rrs_5 was diagnostic for EIB[22].

Several remarks can be made about this study. The MEF_{50} as a measure for airway obstruction should be used with caution due to the large spread in children[21]. However, we found that an increase of 10% of MEF_{50} in % of predicted reduced the risk of the occurrence of EIB by 42% emphasizing the need to evaluate the pre-exercise MEF_{50} in children with asthma.

Due to the intensity of exercise and the cumbersome nature of head gear we chose not to use head gear, leading to an expected upper airway shunt[23]. The lower frequencies are least affected by the upper airway shunt, hence we used lower frequency measurements for analysis (5 Hertz)[24]. The resonance frequency however, may have suffered from this lack of head gear, especially because this study evaluated children, who suffer a stronger upper airway shunt than adults[4].

This study shows that the pre-exercise MEF_{50} is an independent predictor for the occurrence of EIB, emphasizing the importance of close examination of the expiratory flow volume loop. Furthermore, we showed that there is a strong association between BMI and EIB in children with mild to moderate asthma over the full range of BMI. These observations are of clinical relevance since they may provide the clinician with new therapeutic modalities to reduce EIB and improve asthma control.

REFERENCES

1. Godfrey S, Springer C, Novosiki N et al. Exercise but not metacholine differentiates asthma from chronic lung disease in children. Thorax. 1991;46:488-492.
2. Crapo RO, Casaburi R, Coates AL et al. American Thoracic Society. Guidelines for Methacholine and Exercise Challenge Testing. 1999. Am J Respir Crit Care Med. 2000;161:309-329.
3. Linna O. A doctor's ability to assess the severity of childhood asthma by simple clinical features. Acta Paediatr. 2005;94:559-563.
4. Oostveen E, MacLoad D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments Eur Respir J. 2003;22(6):1026-1041.
5. Smith HJ, Reinhold P, Goldman MD. Forced oscillation technique and impulse oscillometry. Eur Repir Mon, 2005;31;72-105.
6. Tantisira KG, Litonjua AA, Weiss ST et al. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP) Thorax. 2003;58:1036–1041.
7. Ulger Z, Demir E, Tanaç R et al. The effect of childhood obesity on respiratory function tests and airway hyperresponsiveness. Turk J Pediatr. 2006;48(1):43-50.
8. Calvert J, Burney P. Effect of body mass on exercise-induced bronchospasm and atopy in African children. J Allergy Clin Immunol 2005;116(4):773-779.
9. Cole TJ, Bellizzi MC, Flegal KM et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ. 2000;320:1240-1243.
10. Eggleston PA, Guerrant JL. A standardized method of evaluating exercise-induced asthma; Journal of allergy and clinical immunology. 1976;58:414-425.
11. Miller MR, Hankinson J, Brusasco V etal. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.
12. Zapletal A, Sama M, Paul T. Lung function in children and adolescents. Methods and reference values In: H. Herzog, editor. Progress in respiratory research; Vol. 22, Basel, Switzerland: S. Karger; 1987, p. 114-218.
13. Chinn S. Obesity and asthma: evidence for and against a causal relation, J Asthma. 2003 Feb;40(1): 1-16.
14. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? Thorax. 2001 Nov;56(11):845-50.
15. Scholtens S, Wijga AH, Seidell JC, et al. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. J Allergy Clin Immunol. 2009 Jun;123(6): 1312-8.e2. Epub 2009 May 5.
16. Camargo CA Jr, Weiss ST, Zhang S, et al. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. Arch Intern Med. 1999 Nov 22;159(21):2582-2588.
17. Lucas SR, Platts-Mills TA. Physical activity and exercise in asthma: relevence to etiology and treatment. J Allergy Clin Immunol. 2005; 115(5): 928-934.
18. Vahlkvist S, Pedersen S, Fitness, daily activity and body composition in children with newly diagnosed, untreated asthma. Allergy 2009;64:1649-1655.
19. Beck KC, Hyatt RE, Mpougas P, et al. Evaluation of pulmonary resistance and maximal expiratory flow measurements during exercise in humans. J Appl Physiol. 1999;86(4):1388-1395.
20. Boulet LP, Turcotte H, Boulet G, et al. Deep inspiration avoidance and airway response to methacholine: Influence of body mass index. Can Respir J. 2005 Oct;12(7):371-376.
21. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–968.

22. Malmberg LP, Mäkelä MJ, Mattila PS, et al. Exercise-induced changes in respiratory impedance in young wheezy children and nonatopic controls. Pediatric Pulmonology 2008; 43:538–544.
23. Marchal F, Mazurek H, Habib M, et al. Input respiratory impedance to estimate hyperreactivity in children: standard method versus head generator. Eur Respir J. 1994;7:601-607.
24. Farré R, Rotger M, Marchal F et al. Assessment of bronchial reactivity by forced oscillation admittance avoids the upper airway artefact. Eur Respir J. 1999;13(4):761-766.