



Airway response to exercise measured by area under the expiratory flow–volume curve in children with asthma

Paweł Majak, MD, PhD^{*}; Łukasz Cichalewski, MD^{*}; Agata Ożarek-Hanc, MD^{*}; Włodzimierz Stelmach, MD, PhD[†]; Joanna Jerzyńska, MD, PhD^{*}; and Iwona Stelmach, MD, PhD^{*}

^{*} Department of Pediatrics and Allergy, Medical University of Lodz, N Copernicus Hospital, Lodz, Poland

[†] Department of Social and Preventive Medicine, Medical University of Lodz, Lodz, Poland

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ABSTRACT

Background: The exercise challenge test is the gold standard for diagnosing exercise-induced bronchoconstriction; however, it produces negative results in many children with postexercise symptoms.

Objective: To assess the utility of the area under the expiratory flow–volume curve (Aex) to identify exercise-induced bronchoconstriction in children with asthma.

Methods: Data from the medical records of 221 children with asthma who underwent an exercise treadmill challenge (ETC) were analyzed. The relation between exercise-induced respiratory symptoms and results of the ETC were assessed, specifically, the maximal decrease in forced expiration in 1 second (FEV₁) and the maximal decrease in the Aex.

Results: The receiver operating characteristic curve showed that a decrease greater than 6% in the Aex was an optimal cutoff point to produce the fewest misclassified ETC results based on a greater than 10% decrease in FEV₁. The results of multivariable logistic regression showed that a decrease greater than 6% in the Aex was comparable to a decrease greater than 10% in FEV₁ during an ETC and was more closely related to the presence of exercise-induced respiratory symptoms. Measuring the Aex during a routine ETC allowed a confirmation of bronchoconstriction in an additional 49 children (44%) with asthma and exercise-induced respiratory symptoms. The Aex measurement increased the sensitivity and negative predictive value of ETC without a significant effect on ETC specificity.

Conclusion: Measuring the Aex increases the sensitivity and negative predictive value of ETC without producing a significant change in ETC specificity. Applying a 6% decrease in the Aex as a cutoff point for a positive exercise challenge test result may prevent the underdiagnosis of exercise-induced bronchoconstriction in children with asthma and postexercise symptoms.

Trial Registration: This study was registered at www.clinicaltrials.gov (NCT01798823).

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Introduction

Physical activity is an important trigger of asthma symptoms in most patients, including children.^{1,2} Exercise-induced bronchoconstriction (EIB) also can indicate a unique asthma phenotype.³ EIB describes a transient narrowing of the airways after vigorous exercise.⁴ EIB occurs in a large proportion of children with asthma, limiting everyday activities that are important for their physical and social development.^{5,6} The exercise challenge test is the gold standard in EIB diagnosis and serves as an objective tool to monitor the protective effect of EIB treatment in children with asthma.⁷

Reprints: Iwona Stelmach, MD, PhD, Department of Pediatrics and Allergy, N Copernicus Hospital, 62 Pabianicka Str 93-513 Lodz, Poland; E-mail: alergol@kopernik.lodz.pl.

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The relatively low sensitivity of the exercise challenge test based on measurements of forced expiration in 1 second (FEV₁) indicates an underdiagnosis of EIB in children with asthma and postexercise symptoms.^{8–10} Considering the high prevalence of postexercise symptoms in children with asthma, the lack of a sensitive tool for the diagnosis of EIB appears to be an important problem for clinicians. Other methods, such as forced oscillation, have been considered ways to improve the sensitivity of the exercise treadmill challenge (ETC).¹⁰

It has been shown that the area under the expiratory flow–volume curve (Aex) after the inhalation of a bronchoconstrictor and several bronchodilators is more suitable in the evaluation of bronchial hyper-reactivity and bronchodilation than the FEV₁.¹¹ However, there are currently few studies using the Aex to evaluate the airway patency of patients with asthma.

Because the various lung function parameters describe unique characteristics of airway obstruction,⁹ it is meaningful to question

the diagnostic value of the Aex compared with the FEV₁ during EIB testing. To the best of the authors' knowledge, a systematic analysis of the diagnostic value of the Aex has not been performed during the diagnosis of EIB in children with asthma.

Therefore, the aim of this study was to assess the utility of the Aex during the diagnosis of EIB in children with asthma.

Methods

Patients

This cross-sectional study evaluated 7- to 17-year-old children with asthma who were recruited from the local pediatric allergology clinic. Data from the medical records of 221 consecutive children with asthma who underwent an ETC were analyzed. A diagnosis of asthma was universally established by the allergist doctors according to symptoms of asthma, physical examination findings of the respiratory system, and improvement of at least 12% in FEV₁ after the administration of salbutamol (200 µg) in all patients.¹

There were 2 groups of patients: (1) children with asthma and exercise-induced respiratory symptoms (EIS group) and (2) children with asthma without any symptoms after exercise (control group). The criteria for inclusion in the EIS group included a medical history of chronic respiratory symptoms (during the previous ≥2 years) and exercise-related wheezing, dyspnea, chest tightness, and cough. The control group included patients whose asthma was in remission (defined according to a set of guidelines¹) and who exhibited a negative medical history for exercise-related symptoms. Patients who met 1 of the exclusionary criteria were not enrolled.

Standardized ETC

Exercise-induced bronchoconstriction was tested using a motor-driven treadmill (Kettler, Ense-Parsit, Germany) according to guidelines of the American Thoracic Society and European Respiratory Society.¹² The children were instructed to run for 8 minutes at a submaximal exercise load. The exercise test consisted of a 2-minute warm-up and 6 minutes of steady-state running on a treadmill. The slope of the treadmill was 5.5% (3°). Small adjustments in the workload (treadmill speed) were made, if necessary, to achieve the targeted heart rates. Nasal clips were used during the test, and heart rate was monitored continuously (electronic heart rate scanner; Kettler). The submaximal run on the treadmill was performed at the same speed (exercise load) for each child. The ambient temperature in the air-conditioned laboratory was kept stable at 22°C, and the humidity remained stable at 40% to 50% throughout the study. Differences of 1°C in temperature and

5 mg H₂O/L in air humidity between patients on a given test day were accepted. FEV₁ was measured before running, immediately after running, and 3, 6, 10, 15, 20, and 30 minutes after running. The maximum percentages of decrease in the FEV₁ and Aex after the exercise test were calculated using the following formula: [(pre-exercise value – lowest postexercise value)/pre-exercise value] × 100. Spirometry was performed using a Master Screen unit (Erich Jaeger GmbH-Hochberg, Germany). The spirometer automatically calculated the Aex.

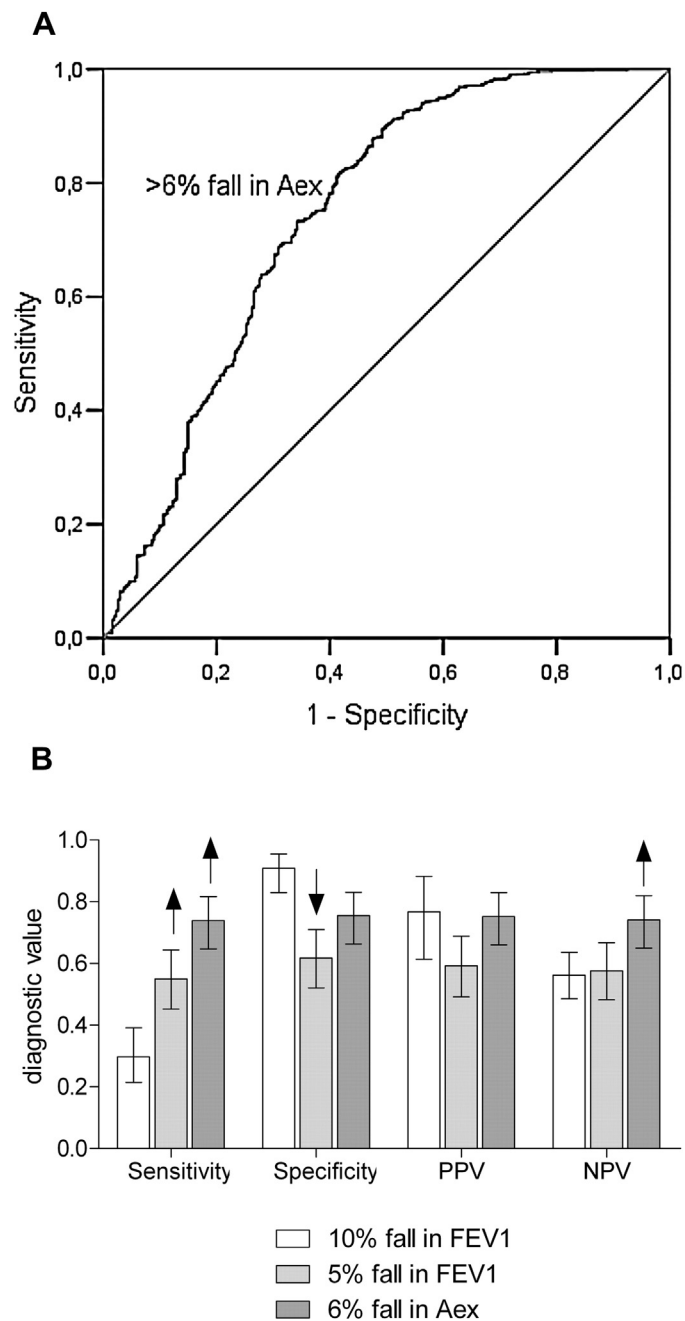


Figure 1. (A) Receiver operating characteristic curve shows that a decrease greater than 6% in the area under the expiratory flow–volume curve (Aex) is an optimal cutoff point to identify positive (based on >10% decrease in forced expiration in 1 second) exercise treadmill challenge results. (B) Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of exercise treadmill challenge with a greater than 10% decrease in forced expiration in 1 second (reference), a 5% decrease in forced expiration in 1 second, and a greater than 6% decrease in Aex. Black arrows indicate significant differences from the reference criterion of positive exercise treadmill challenge results.

Table 1
Baseline characteristics

	Control (n = 110)	EIS (n = 111)	P value
Age (y), mean ± SD	12.3 ± 3.2	13.3 ± 3.1	.015
Boys, n (%)	60 (54.5)	47 (42.3)	.070
Asthma duration (y), median (quartile range)	4 (1–7)	4 (0–8)	.702
BMI (kg/m ²), mean ± SD	20.7 ± 4.0	21.3 ± 4.0	.242
Atopy, n (%)	72 (65.5)	58 (52.3)	.046
Allergen immunotherapy, n (%)	51 (46.8)	29 (26.1)	.001
Pre-exercise FEV ₁ (% predicted), mean ± SD	101.5 ± 14	105.1 ± 13.6	.053
ICS dose ^a (µg), median (quartile range)	0 (0–200)	400 (200–400)	<.001
Long-lasting β ₂ -agonist add-on therapy, n (%)	1 (0.9)	55 (49.5)	<.001
Antileukotriene therapy, n (%)	14 (12.7)	57 (51.4)	<.001

Abbreviations: BMI, body mass index; EIS, exercise-induced symptoms; FEV₁, forced expiration in 1 second; ICS, inhaled corticosteroid; SD, standard deviation.

^aDaily dose of budesonide or daily equivalent.

Cutoff Points for Maximal Decrease in FEV₁

The literature supports various cutoff points; 9% to 10% represent typical decreases in the clinical category.⁷ In the present study, a 10% decrease in FEV₁ during an ETC was applied as a reference point for clinical significance. Owing to the low sensitivity of a 10% decrease in FEV₁, the Aex was proposed as a new marker. As a comparative strategy, the clinical utility of a 5% decrease in FEV₁ (arbitrarily chosen) was analyzed in the same study population to show that applying the same strategy with a different FEV₁ decrease does not resolve the low sensitivity of an ETC.⁸

Ethics

The study was approved by the Medical University of Lodz ethics committee. Written consent was obtained from the patients and their parents.

Statistical Methods

The associations between the presence of exercise-induced respiratory symptoms (EIS vs control group, defined as the dependent variable) and the decrease in FEV₁ (dichotomized at cutoff points of >10% and >5%) and a decrease greater than 6% in the Aex were analyzed using multivariable logistic regression. The results were adjusted for the effect of potential confounders. The Aex cutoff point for optimal discrimination (highest sensitivity and specificity) between patients with and those without positive ETC results was calculated using receiver operating characteristics curve analysis. Comparisons between groups were assessed using the Mann-Whitney test or χ^2 test. All statistical analyses were performed using StatSoft Statistica 8.0 for Windows (StatSoft, Inc, Tulsa, Oklahoma). A *P* value less than .05 was used to indicate statistical significance.

Results

The data from all 221 children were included in the analysis. Detailed characteristics of the included patients are listed in Table 1. Compared with patients in the control group, patients in the EIS group were older, treated with specific immunotherapy less frequently, and observed to have atopy less frequently. In addition, patients with exercise-induced respiratory symptoms were treated with a higher inhaled corticosteroid dose and more frequently received long-acting β agonist and/or leukotriene receptor antagonists compared with patients in the control group.

A 3-step analysis was followed to assess the clinical value of the Aex value during an ETC to diagnose exercise-induced respiratory symptoms in children with asthma.

In the first step, the Aex cutoff point that offered optimal discrimination (highest sensitivity and specificity) between patients with and those without a positive ETC result was calculated.

A decrease greater than 6% in the Aex was most closely related to the ETC outcome (based on >10% decrease in FEV₁; Figure 1A).

In the second step, the associations between the presence of exercise-induced respiratory symptoms (EIS vs control group: defined as the dependent variable) and the decrease in FEV₁ (dichotomized at cutoff points >10% and >5%) and the greater than 6% decrease in the Aex as calculated during the ETC were compared (Table 2). The multivariable logistic regression showed that the greater than 6% decrease in the Aex during the ETC was more closely related to the presence of exercise-induced respiratory symptoms than was the greater than 10% decrease in FEV₁. No significant associations between the presence of exercise-induced respiratory symptoms and the greater than 5% decrease in FEV₁ during the ETC were observed. These relations were independent of age, sex, atopy/immunotherapy, inhaled corticosteroid dose, long-acting β 2-agonist add-on therapy, or antileukotriene therapy. The potential confounders were chosen according to the results of a baseline comparison between the EIS and control groups (Table 1).

In the third step, a greater than 6% decrease in the Aex yielded a significantly higher sensitivity and a higher negative predictive value in the diagnosis of EIB compared with a greater than 10% decrease in FEV₁ (gold standard of EIB diagnosis; Table 2, Fig 1B). Importantly, the greater than 6% decrease in the Aex did not show a significantly lower specificity compared with the greater than 10% decrease in FEV₁ (Fig 1B). In addition, a higher sensitivity and a significantly lower specificity of a greater than 5% decrease in FEV₁ compared with a greater than 10% decrease were observed during the diagnosis of EIB (Fig 1B). Measuring the Aex during a routine ETC allowed the confirmation of bronchoconstriction in an additional 49 children (44%) with asthma and exercise-induced respiratory symptoms (EIS group) and avoided EIB identification in 17 children (15%) without symptoms and with negative ETC results based on the greater than 10% decrease in FEV₁ (control; Table 2).

Discussion

This study was performed to establish the possible role of Aex measurement during ETC while diagnosing EIB in children with asthma. The Aex increased the sensitivity and negative predictive value of the ETC without significantly affecting the specificity. Changing the cutoff value for the decrease in FEV₁ (from 10% to 5%) increased the sensitivity of the ETC and simultaneously significantly decreased the specificity, effectively neutralizing the clinical value. The clinical utility of a 5% decrease in FEV₁ was analyzed only as a comparative strategy to show that changes in the FEV₁ decrease do not resolve the problem of low sensitivity for the ETC.

Measuring Aex during a routine ETC allowed the confirmation of bronchoconstriction in an additional 49 children (44%) with asthma and exercise-induced respiratory symptoms.

Table 2

Exercise-induced maximal decrease in FEV₁ and Aex by study group^a

	Control, n (%)	EIS, n (%)	OR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<10% decrease in FEV ₁ (% predicted)	100 (90.9)	78 (70.3)	ref	0.30 (0.21–0.39)	0.91 (0.82–0.96)	0.77 (0.61–0.88)	0.56 (0.49–0.64)
≥10% decrease in FEV ₁ (% predicted)	10 (9.1)	33 (29.7)	4.11 (1.14–14.88)				
<5% decrease in FEV ₁ (% predicted)	68 (61.8)	50 (45.0)	ref	0.55 (0.45–0.64)	0.62 (0.52–0.71)	0.59 (0.49–0.69)	0.58 (0.48–0.67)
≥5% decrease in FEV ₁ (% predicted)	42 (38.2)	61 (55.0)	1.61 (0.67–3.86)				
<6% decrease in Aex (L ² /s)	83 (75.5)	29 (26.1)	ref	0.74 (0.65–0.82)	0.75 (0.66–0.83)	0.75 (0.66–0.83)	0.74 (0.65–0.82)
≥6% decrease in Aex (L ² /s)	27 (24.5)	82 (73.9)	8.22 (3.12–21.68)				

Abbreviations: Aex, area under the expiratory flow–volume curve; CI, confidence interval; EIS, exercise-induced symptoms; FEV₁, forced expiratory flow in 1 second; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; ref, reference value.

^aThe associations between the presence of exercise-induced symptoms (EIS vs control group) and maximal decrease in FEV₁ (different cutoffs >5% and >10%) and maximal decrease in Aex are presented as ORs (95% CIs). ORs were adjusted to incorporate the effects of age, atopy/immunotherapy, inhaled corticosteroid dose, long-acting β 2-agonist therapy, or antileukotriene therapy. Maximum percentage decrease in FEV₁ and Aex after exercise testing was calculated using the following formula: [(pre-exercise value – lowest postexercise value)/pre-exercise value] × 100. The dependent variable was exercise-induced symptoms.

Seppala¹³ used Aex to measure the response of airways to methacholine in healthy subjects and established a higher sensitivity in the Aex than in FEV₁ and midexpiratory flows. The present results suggest that the Aex can be considered a sensitive, simple, and reliable parameter to measure the response to exercise in children with asthma. There are several explanations for the greater sensitivity of Aex in the evaluation of induced bronchoconstriction. First, the Aex provides information on central and peripheral airway obstructions. Second, it reflects air flow and forced vital capacity changes in response to a residual volume increase or decrease during forced expiration. Third, the Aex measurement is affected by airway obstruction during the complete forced expiratory maneuver. In contrast to the Aex, FEV₁ reflects changes in the airway patency at approximately 80% to 90% of forced vital capacity in most healthy children.¹⁴

Although this study showed the significant value of the Aex for diagnosing EIB in children with asthma, this parameter is not a specific feature of patients with asthma because its pattern and magnitude change after bronchodilation.¹¹

The observation of a lower prevalence of atopy in the EIS vs control group requires discussion. This observation could be explained by the fact that most patients in the control group did not present any asthma symptoms despite not taking controller medications and had been recruited from successfully desensitized children. Consequently, atopy was less frequent in the EIS group.

Although not all patients with asthma and exercise-induced respiratory symptoms present bronchoconstriction after exercising, the low sensitivity of FEV₁ during the ETC suggests the potential for underdiagnosis of EIB. The lack of an objectively confirmed diagnosis of EIB has important clinical consequences; therefore, the authors suggest measuring the Aex during a routine ETC to prevent the underdiagnosis of EIB.

Including an Aex measurement increases the sensitivity and negative predictive value of the ETC without a significant change in ETC specificity. Using a 6% decrease in the Aex as a cutoff point for a positive exercise challenge outcome may prevent the

underdiagnosis of EIB in children with asthma and postexercise symptoms.

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