Efficient Use of Simple Exercise-Induced Bronchoconstriction Challenge Testing in Pediatric Exercise-Induced Dyspnea

Rajeev Bhatia and Emma Schwendeman

BACKGROUND: A simple exercise test to evaluate for exercise-induced bronchoconstriction (EIB) is routinely ordered in pediatric patients with exercise-induced dyspnea. However, the utility of this test in establishing the cause of exercise-induced dyspnea is not thoroughly examined in the pediatric population. We sought to assess the efficiency of a simple EIB challenge test in finding the cause of exercise-induced dyspnea in pediatric patients referred to our tertiary center in the last 5 y. METHODS: We performed a retrospective chart review for all of these exercise tests done at Akron Children's Hospital from March 2011 to March 2016. Patients with chronic conditions (eg, cystic fibrosis, cardiac abnormality) were excluded. Demographics, clinical diagnosis of asthma, a presumptive diagnosis of exercise-induced asthma or EIB by the referring provider, symptoms with and without exercise, albuterol use, spirometry, and simple EIB challenge test results were collected. The chi-square test of independence was utilized in the examination of potential dependent relationships between categorical variables. A *P* value < .05 was considered to be statistically significant. RESULTS: Out of 164 enrolled subjects (57 males; age 6–20 y), only 19% showed evidence of EIB. There were no significant associations between EIB status (ie, EIB-positive or EIB-negative) based on exercise testing and gender, typical symptoms of EIB, diagnosis of exercise-induced asthma or EIB, and albuterol use (*P* > .05). However, a subject without asthma was 2.8 times more likely to have negative exercise test for EIB (odds ratio 2.8, 95% CI 1.3–6.5); in addition, approximately 85% of tests in subjects without asthma were negative. CONCLUSION: In a majority of subjects without asthma, a simple EIB challenge testing failed to uncover the cause of exercise-induced dyspnea and thus was inefficient. In these subjects, cardiopulmonary exercise testing may be more useful and cost-effective to explore other causes of dyspnea including EIB. *Key words: pediatric exercise-induced dyspnea; exercise- induced bronchoconstriction; exercise- induced asthma; exercise test; pediatric asthma; cardiopulmonary exercise test*. [Respir Care 2019;64(1):71–76.
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Introduction

Exercise-induced bronchoconstriction (EIB) or exercise-induced asthma are the most commonly suspected diagnoses for exercise-induced dyspnea in pediatric patients with or without asthma.[1,2] EIB and exercise-induced asthma are often used interchangeably. However, many experts recommend using the term EIB instead of exercise-induced asthma because EIB does not imply that exercise caused asthma or the patient has underlying asthma.[3] Providers often recommend a therapeutic trial of albuterol for children or adolescents complaining of dyspnea with exercise and initiate appropriate therapy for those who ben-

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efit. If a response to albuterol is unclear, providers may order a simple EIB challenge test, which involves exercising on a treadmill or bike. Serial spirometry after exercise is used to determine whether EIB is present and to quantify the severity of the disorder.[4] This test is limited to the examination of the presence or absence of EIB. Alternatively, providers may opt to order more comprehensive cardiopulmonary exercise testing (CPET). With CPET, multiple parameters are continuously recorded, providing a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems.[5,6]

Which of these tests is most appropriate may not be obvious. While the simple EIB challenge is less expensive and more widely available, a negative simple EIB challenge typically provides no clue to the ordering physician regarding the cause of exercise-induced dyspnea. CPET, while more expensive and labor-intensive, is much more likely to provide evidence of other causes of exercise-induced dyspnea in addition to EIB (eg, physiological limitation, deconditioning, exercise-induced hyperventilation, vocal cord dysfunction, supraventricular tachycardia).

One factor that influences which of these 2 tests is most appropriate is the likelihood that the simple exercise challenge test will be positive. If the test is positive, the provider will establish a diagnosis of EIB with the least expense and technical complexity. On the other hand, if the test is unlikely to be positive (ie, EIB is unlikely based on clinical judgment), the provider might opt to order the more expensive test. This is obviously the case when the clinical characteristics of the exercise intolerance suggest causes other than EIB or the condition seems multifactorial.

After a literature review, we found that the efficiency of simple EIB challenge testing in establishing the cause of exercise-induced dyspnea is not thoroughly examined in the pediatric population. In this retrospective study, we investigated the efficiency of simple EIB challenge testing in finding the cause of exercise-induced dyspnea in patients referred to our tertiary center over the last 5 years.

QUICK LOOK

Current knowledge

A simple exercise test to evaluate for exercise-induced bronchospasm (EIB) is routinely ordered in pediatric patients with exercise-induced dyspnea. However, the efficiency of this test in establishing the cause of exercise-induced dyspnea has not been thoroughly examined in a pediatric population.

What this paper contributes to our knowledge

In the majority of subjects without asthma, simple EIB challenge testing failed to reveal the cause of exercise-induced dyspnea and thus was inefficient: 7 of 8 subjects (85%) without a clinical diagnosis of asthma showed no evidence of EIB, thus the cause of exercise-induced dyspnea was not clear despite simple EIB challenge testing.

Methods

We performed a retrospective chart review for all of the simple EIB challenge tests conducted at Akron Children's Hospital from March 2011 to March 2016. The inclusion criteria were pediatric patients age 6–21 y.[7] Patients with chronic conditions (eg, cystic fibrosis, cardiac abnormality, joint/bone disease) were excluded. Subjects with a diagnosis of asthma were not excluded. Demographics, duration of baseline symptoms, symptoms with and without exercise, use of albuterol, baseline spirometry and exercise test results, as well as the diagnosis of asthma, exercise-induced asthma, or EIB by the referring provider were collected. Patients who did not have the above information based on extensive retrospective chart review were also excluded. Exercise testing was done according to American Thoracic Society guidelines.[4] The subject was asked to walk or run on a treadmill. Starting at a low speed and grade, both were progressively advanced during the first 2–3 min of exercise until the heart rate was 80–90% of the predicted maximum (calculated as 220 − age in years). The subject was encouraged to exercise until exhaustion. Spirometry was done prior to the test and at 0, 5, 10, and 15 min following exercise and was reported based on standard reference values.[8,9] A drop of 10% or more in FEV_1 post-exercise was taken as a positive test for EIB.

Summary statistics for continuous variables of interest were examined as well as distributional shape. Frequencies and percentages for categorical outcome variables were calculated. Analysis focused on differences and relationships between the demographic and clinical variables described above and a positive exercise challenge. For continuous data, the distribution-based independent sample *t* test with variance assessment was used to assess potential differences in patient characteristics. The Wilcoxon rank-sum test was performed to account for small departures of normality where appropriate, with similar results seen. The chi-square test of independence was utilized in the examination of potential dependent relationships between categorical variables. In cases of cell counts at or below $n = 5$, the Fisher exact test was used. Statistical analyses were completed using SAS 9.4/13.2 (SAS Institute, Cary, North Carolina). Unless otherwise noted, all testing was 2-tailed and evaluated at the type-1 error rate of $\alpha = 0.05$ level of statistical significance. The Akron Children's Hospital institutional review board reviewed and approved the study.

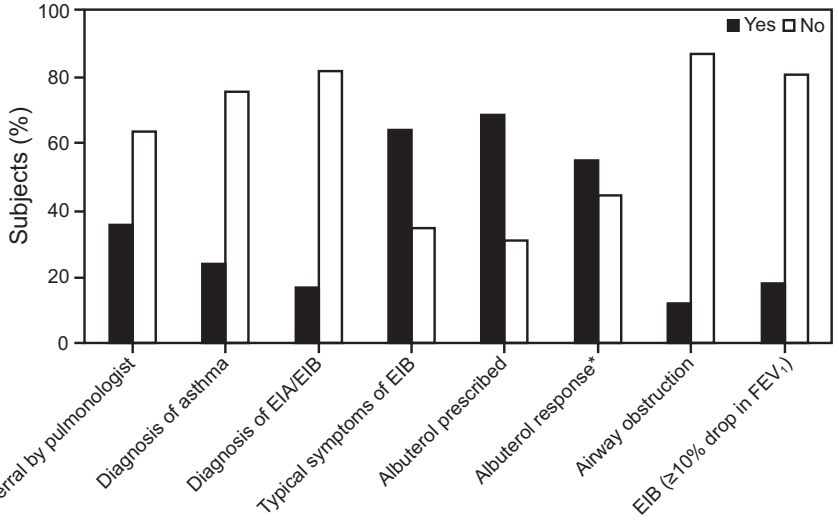

Fig. 1. Characteristics of study population as well as EIB results based on simple EIB challenge testing (N = 164 subjects). * Albuterol response (n = 96 subjects) among subjects who were prescribed albuterol prior to the test. EIA = exercise-induced asthma, EIB = exercise-induced bronchoconstriction.

Results

A total of 455 medical charts were evaluated, but only 164 subjects (57 males) fulfilled the inclusion criteria. Subjects had a mean± SD age of 13.5 ± 3.1 y (range 6–20 y). The majority were excluded because of insufficient information available about their medical history as well as the reason for referral. Of the 164 selected subjects, 59 (36%) had been referred by pulmonologists at Akron Children's Hospital. The remainder had been referred by outside providers (pediatricians, family medicine practitioners, nurse practitioners). Forty (24%) had been assigned a diagnosis of asthma at the time of referral by their provider, and 29 (17%) had a presumptive diagnosis of exercise-induced asthma or EIB. In addition, 106 (65%) subjects reported typical symptoms of EIB (eg, cough, chest tightness, wheezing) 67 (41%) subjects also had respiratory symptoms without activity. The mean± SD duration of symptoms prior to testing was 9.3 ± 14.7 months. Almost 70% of subjects (n = 113) were prescribed albuterol prior to the test, with an almost equal number of responders and non-responders (55% vs 45%). The majority had normal baseline spirometry, and 21 (13%) subjects showed some degree of airway obstruction (Fig. 1).

Only 31 (19%) subjects demonstrated EIB on simple EIB challenge testing, whereas 133 (81%) subjects showed no evidence of EIB (Fig. 1). There was no difference in demographic variables, clinical symptoms, and baseline spirometry between the positive and negative EIB groups (Table 1). Duration of symptoms was also not different between the groups. Female gender, referral by a pulmonologist, and history of albuterol use increased the likelihood of a positive EIB test based on chi-square test of independence, however the results were inconclusive (Table 2). Fisher exact test, which is more conservative, did not show dependence between these characteristics and the likelihood of positive EIB results (Table 2).

The only parameter associated with an increase or decrease in the likelihood of positive EIB results was a clinical diagnosis of asthma at the time of the test. The dependent relationship between EIB (+/−) status and asthma diagnosis (−/+) (P = .01) had an associated odds ratio of 2.8 (95% CI 1.3–6.5), that is a subject without asthma was 2.8 times more likely to have a negative EIB challenge test than a subject with asthma. Our results showed that 85% (106/124) of subjects with no prior diagnosis of asthma had a negative EIB challenge test in contrast to 67% (27/40) of subjects in the asthma group (Table 2, Fig. 2).

Discussion

In the majority of subjects, simple EIB challenge testing failed to reveal the cause of exercise-induced dyspnea. This failure rate was exaggerated in subjects without asthma. Seven of 8 subjects (85%) without a clinical diagnosis of asthma showed no evidence of EIB, thus the cause of exercise-induced dyspnea was not diagnosed despite simple EIB challenge testing. Interestingly, the results of simple EIB challenge testing did not depend on whether a subject had typical symptoms of EIB (eg, chest tightness, cough, wheezing), whether a subject had a presumptive diagnosis of exercise-induced asthma or EIB, or whether a subject had tried albuterol in the past. Therefore, in our study, a clinical diagnosis of asthma was the only patient

Table 1. Demographic and Spirometry Measurements and Comparison Between EIB-Positive and EIB-Negative Groups

Variables	All Subjects	EIB-Positive Group	EIB-Negative Group	*P**
Age, y	13.5 ± 3.1 (6–20)	14.3 ± 2.8 (6–19)	13.3 ± 3.1 (6–20)	.09
Weight, kg	55.9 ± 17.2 (19.2–106.6)	55.7 ± 16.5 (19.2–105.4)	56 ± 17.4 (23.3–106.6)	.92
Height, cm	159.2 ± 14.6 (116–192)	160 ± 12.4 (116–177)	159 ± 15.1 (122–192)	.73
Body mass index, kg/m^2	21.6 ± 4.6 (13.4–38.7)	21.6 ± 5.4 (14.3–38.5)	21.6 ± 4.4 (13.4–38.7)	.97
FEV_1, % pred	100.6 ± 11.6 (70–130)	98.5 ± 11.1 (74–120)	101.6 ± 11.6 (70–130)	.25
FVC, % pred	102.6 ± 11.4 (68–144)	100.4 ± 12.2 (68–123)	103.1 ± 11.2 (80–144)	.23
FEV_1/FVC, %	85.7 ± 5.8 (67–100)	86.5 ± 6.4 (74–98)	85.5 ± 5.7 (67–100)	.40
$FEF_{25–75\%}$, % pred	97.8 ± 21.6 (46–166)	95.1 ± 20.8 (46–142)	98.4 ± 21.9 (48–166)	.44

N = 164 subjects; EIB-positive group, n = 31 subjects; EIB-negative group, n = 133 subjects. Values are shown as mean ± SD (range).
* P value defines comparison between EIB positive vs. EIB negative group.
EIB = exercise-induced bronchoconstriction
$FEF_{25–75\%}$ = forced expiratory flow during the middle half of the FVC maneuver

Table 2. Frequency Distributions as Well as Relationship Between Variables and Simple EIB Challenge Results

	EIB-Positive Group	EIB-Negative Group	Total	*P**	*P*†
Gender				.046	.059
Male	6 (10%)	51 (90%)	57		
Female	25 (23%)	82 (77%)	107		
Referral by				.044	.061
Pulmonologist	16 (27%)	43 (73%)	59		
Nonpulmonologist	15 (14%)	90 (86%)	105		
Albuterol prescribed				.046	.053
Positive	26 (23%)	87 (77%)	113		
Negative	5 (10%)	46 (90%)	51		
Diagnosis of asthma				.01	
Positive	13 (33%)	27 (67%)	40		
Negative	18 (15%)	106 (85%)	124		

The P value defines the relationship between exercise challenge results and the variables; eg, the dependent relationship between gender and EIB results was inconclusive based on chi-square test (* P = .046), while the Fisher exact test provided evidence against it († P = .059).

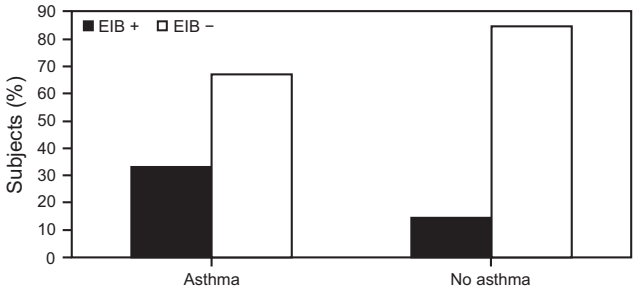

Fig. 2. Proportion of EIB-positive and EIB-negative subjects (based on simple exercise challenge testing) in subjects with and without asthma.

characteristic that increased or decreased significantly the likelihood of a positive simple EIB challenge test.

As mentioned previously, a high rate of negative exercise tests decreases the usefulness of simple EIB challenge testing. The negative EIB testing could be useful in a minority of the subjects, but in most cases a negative test is not helpful for the ordering provider. In 4 of 5 subjects in our study, this test was not helpful in finding the cause of exercise-induced dyspnea. Simple EIB challenge testing is most efficient in finding the cause of exercise-induced dyspnea if the likelihood of the test being positive is higher at the time of ordering the test. The only variable that increased or decreased the likelihood of a positive test in our study was the diagnosis of asthma. A patient without asthma was almost 3 times more likely to have a negative test for EIB. In these subjects, simple EIB challenge testing is much less likely to be helpful, being positive in only 1 of 8 such subjects in our population (Fig. 2). In subjects without asthma, simply identifying the absence of EIB does little to point toward further management. These patients are much more likely to benefit from comprehensive evaluation with CPET instead of simple EIB challenge testing.

The studies in which CPET was utilized for detailed assessment of exercise symptoms in pediatric subjects with

exercise-induced dyspnea have also shown that very few of these subjects demonstrate EIB.[1,2,10-12] The majority of these subjects have another cause of dyspnea, such as physiological limitation, vocal cord dysfunction, deconditioning, restrictive abnormalities, exercise-induced hyperventilation, or supraventricular tachycardia. More than half (52%) of the subjects of a group similar to ours showed normal physiological limitation on CPET.[1] The dyspnea in these healthy patients is likely related to an excessive psycho-physiological sensation of the perceived work of breathing with increased ventilation.[13] Patients who demonstrate deconditioning are given a graded exercise regimen, whereas patients with vocal cord dysfunction and exercise-induced hyperventilation are referred to a speech therapist/psychologist for breathing and self-regulation techniques.[14,15] Patients with evidence of a cardiac abnormality (abnormal electrocardiogram or an excessive increase in heart rate with increasing work load) are referred for evaluation by a cardiologist,[16] and those with pulmonary limitation are best referred to a pulmonologist.[12]

The cost effectiveness and availability of CPET could be a limiting factor, and taking into account all the unnecessary treatments and provider visits (especially to the subspecialists) for these patients, the benefits outweigh the risk/cost. Although the cost of simple EIB challenge testing is one fourth of that of CPET, as shown in our study of subjects without asthma, it failed to provide the cause of exercise-induced dyspnea in 7 of 8 tests, making it eventually cost-ineffective compared to CPET. Although previous studies have also shown a low rate of positive EIB tests, none have provided recommendations regarding the choice of the test.[2,10,17]

An EIB-positive rate of only 19% in our subject population is in accordance with EIB reported in other similar studies.[17] A prospective study done in Vancouver school children showed evidence of EIB in 15.4% of subjects based on exercise testing.[2] Similarly, in another prospective study, Mahut et al[10] found EIB in only 17 (21.5%) of 79 otherwise healthy children evaluated for exertional dyspnea. In our study 65% of subjects were reported to have typical symptoms of EIB based on history, but $< 20\%$ showed evidence of EIB on exercise testing. This is not surprising as many studies have shown poor correlation between self-reported symptoms and EIB based on positive exercise testing.[3,18,19]

Limitations to this study include those inherent in an exploratory analysis on a retrospective chart review. No data were available to use in an a priori sample-size analysis. Therefore, this study was not necessarily fully powered for the analysis of a specific hypothesis and, as such, the results may not be fully generalizable. We could not confirm or refute the diagnosis of asthma or EIB given by the referring provider based on history. However, the reliability of a diagnosis of asthma based on history is much more accurate than diagnosis of EIB based on history.[20,21] We were also unable to classify the subjects based on severity of asthma, as these data were unavailable for most of the subjects, given the study was a retrospective chart review. The low numbers of males is in line with other studies that have shown increased reporting of exercise-induced dyspnea in female subjects.[22] We could not differentiate between athlete and non-athlete subjects. The likelihood of EIB without asthma in athlete subjects is more than in non-athletes without asthma.[23,24] Finally, protocol at our institution is to perform post-exercise spirometry at 0, 5, 10, and 15 min post-exercise and not at 30 min post-exercise. This might have led to missing some true cases of EIB because bronchoconstriction can happen later in some cases.[4] Despite the above limitations, the evidence of inefficiency of simple EIB challenge testing in pediatric subjects without a diagnosis of asthma seems clear from our data.

Conclusion

In the majority of subjects without asthma, simple EIB challenge testing failed to uncover the cause of exercise-induced dyspnea in our study. Thus, simple EIB challenge testing is likely to be inefficient and cost-ineffective in pediatric exercise-induced dyspnea patients without asthma because the results are likely to be negative in most of these patients. In these patients, CPET along with pre- and post-exercise spirometry may be more useful and cost-effective in exploring alternative causes of dyspnea including EIB, especially in patients with persistent symptoms and significant parental concern.

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