Diagnostic accuracy of the bronchodilator response in children

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Background: The bronchodilator response (BDR) reflects the reversibility of airflow obstruction and is recommended as an adjunctive test to diagnose asthma. The validity of the commonly used definition of BDR, a 12% or greater change in FEV_1 from baseline, has been questioned in childhood.
Objectives: We sought to examine the diagnostic accuracy of the BDR test by using 3 large pediatric cohorts.
Methods: Cases include 1041 children with mild-to-moderate asthma from the Childhood Asthma Management Program. Control subjects (nonasthmatic and nonwheezing) were chosen from Project Viva and Home Allergens, 2 population-based pediatric cohorts. Receiver operating characteristic curves were constructed, and areas under the curve were calculated for different BDR cutoffs.
Results: A total of 1041 cases (59.7% male; mean age, 8.9 ± 2.1 years) and 250 control subjects (46.8% male; mean age, 8.7 ± 1.7 years) were analyzed, with mean BDRs of 10.7% ± 10.2% and 2.7% ± 8.4%, respectively. The BDR test differentiated asthmatic patients from nonasthmatic patients with a moderate accuracy (area under the curve, 73.3%). Despite good specificity, a cutoff of 12% was associated with poor sensitivity (35.6%). A cutoff of less than 8% performed significantly better than a cutoff of 12% ($P = .03$, 8% vs 12%).
Conclusions: Our findings highlight the poor sensitivity associated with the commonly used 12% cutoff for BDR. Although our data show that a threshold of less than 8% performs better than 12%, given the variability of this test in children, we conclude that it might be not be appropriate to choose a specific BDR cutoff as a criterion for the diagnosis of asthma. (J Allergy Clin Immunol 2013;132:554-9.)

Key words: *Asthma, bronchodilator response, diagnosis*

In asthmatic patients the response to bronchodilators reflects the reversibility of airway airflow obstruction. High bronchodilator response (BDR) in asthmatic patients has been associated with poor clinical outcomes,[1] increased airway inflammation,[2] and increased response to inhaled corticosteroids,[1,3] supporting that BDR has prognostic and therapeutic relevance. The BDR test provides additional information to the clinical history and is recommended by international guidelines as an adjunct to the clinical history in the diagnosis of asthma.[4]

BDR can be expressed by using different methods, with the 3 most common being the percentage of FEV_1, the percentage of the initial predicted value for FEV_1, and absolute change in FEV_1 after administration of a short-acting bronchodilator. A significant BDR is commonly defined as a 12% or greater and 200 mL or greater change in FEV_1 from baseline.[5] This 12% criterion, which was recently reaffirmed in a large international study,[6] approximates the 95th percentile for percentage change in FEV_1 after bronchodilator administration in general population studies, which mainly consist of adults.[7] The forced oscillation technique, which provides information on airway resistance and reactance, has also been used to measure response to bronchodilators and to differentiate between asthmatic and nonasthmatic patients,[8,9] especially in younger children who are unable to cooperate during spirometric testing. However, this technique is not widely used because standardized guidelines are lacking.

Although the National Asthma Education and Prevention Program's Expert Panel Report 3 uses the 12% cutoff as evidence of airway reversibility in establishing the diagnosis of asthma[4] and this cutoff is used to include subjects in several childhood asthma trials,[10,11] the validity of the 12% cutoff has been questioned in the pediatric population.[12] BDR tends to increase with decreasing baseline FEV_1.[13] In subjects with low baseline FEV_1, small changes in absolute FEV_1 in response to a bronchodilator translate into large percentage changes in FEV_1. Because most children with asthma have baseline FEV_1 within the normal reference range, the increase in FEV_1 after bronchodilator administration is limited. Dundas et al[14] suggest that a 9% or greater

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Abbreviations used
AUC: Area under the curve
BDR: Bronchodilator response
CAMP: Childhood Asthma Management Program

increase in FEV_1 provided the most acceptable sensitivity (50%) and specificity (86%) to detect previous wheeze in 5- to 10-year-old children. These results were corroborated by a more recent study showing that a BDR of 9% or greater was optimal at differentiating asthmatic from nonasthmatic children with similar sensitivity and specificity.[12] This study was performed in a predominantly Hispanic cohort and thus might have limited generalizability to children of other ethnicities.

In this study we determined the BDR cutoff that best differentiates between children with mild-to-moderate asthma and children without asthma in a large and predominantly white population. We hypothesized that a BDR cutoff of 12% would be specific but not sufficiently sensitive for diagnosing asthma in children.

METHODS

Subjects

Participants from 3 pediatric cohorts were included in this study. Asthma cases consisted of children enrolled in the Childhood Asthma Management Program (CAMP). The demographics of the CAMP subjects and the study design have been previously reported.[15] Briefly, this multicenter trial randomized 1041 children with mild-to-moderate asthma aged 5 to 13 years to budesonide, nedocromil, or placebo. Children were included if they had asthma symptoms 2 or more times per week, used an asthma medication daily, or used an inhaled bronchodilator twice per week for 6 or more months and had a positive methacholine challenge test result. The long-term effects of these treatments on lung growth were evaluated.[15] Follow-up visits occurred at 2 and 4 months after randomization and every 4 months thereafter for an average of 4.3 years.

The control patients for this study were selected from 2 pediatric general population cohorts. Project Viva is a prospective cohort study examining the effect of prenatal and perinatal factors on maternal and child health. Details of the study design have been described previously.[16] This prebirth cohort consisted of 2128 singleton infants, the mothers of whom were recruited from Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts. Of these children, 1116 attended Project Viva's 7-year in-person visit, 819 of whom attempted the BDR test and 468 had valid results. The Home Allergens cohort is a birth cohort of children with a parental history of allergy or asthma. Details of the study design have been published.[17] Five hundred five infants were recruited within 48 hours of birth in the metropolitan Boston area. Telephone questionnaires about symptoms and diagnoses of atopic disease were administered every 2 months for the first 2 years of life and then every 6 months. A total of 284 children were followed until age 12 years, when 250 of them performed the bronchodilator test. Subjects from these 2 population-based cohorts were selected as control subjects if they had never been given a diagnosis of asthma or had never wheezed, both assessed through a questionnaire or interview ($n = 197$ in Project Viva and $n = 53$ in Home Allergens).

In all 3 cohorts the children's parents or guardians provided informed consent, and the study was approved by the respective local institutional review board.

Spirometry and BDR

In CAMP the BDR test was performed at randomization and at subsequent visits during which a methacholine challenge was not administered.[18] Spirometry was performed at least 4 hours after the last use of a short-acting bronchodilator and at least 24 hours after the last use of a long-acting bronchodilator. For the purpose of this analysis, we used the BDR test at randomization, at which point subjects had been off their regular asthma medications for at least 28 days but were allowed to use a rescue bronchodilator and prednisone, if needed. The BDR test was performed around age 7 years for Project Viva (range, 6.6-10.9 years) and at age 12 years for Home Allergens (range, 11.1-12.7 years). In Project Viva spirometry was performed with the EasyOne Spirometer (NDD Medical Technologies, Andover, Mass). In Home Allergens spirometry was performed by using the Eagle+ spirometer (Collins Medical, Louisville, Colo). In all 3 cohorts postbronchodilator spirometric measures were obtained at least 15 minutes after administration of 2 puffs (90 μg per puff) of albuterol. Spirometric performance was required to meet American Thoracic Society criteria for acceptability and reproducibility, with each subject producing at least 3 acceptable spirograms, 2 of which must have been reproducible.[19]

In this study we defined BDR as a percentage change in absolute FEV_1 after albuterol administration, as follows:

$$(\text{Postbronchodilator } FEV_1 - \text{Prebronchodilator } FEV_1)/\text{Prebronchodilator } FEV_1 \times 100.$$

Given the lack of consensus in the definition of BDR, we have also calculated BDR as a percentage of the initial predicted value for FEV_1 in CAMP, as follows:

$$(\text{Postbronchodilator } FEV_1 - \text{Prebronchodilator } FEV_1)/\text{Prebronchodilator percent predicted } FEV_1 \times 100$$

and compared it with the former definition.

Statistical analysis

A descriptive analysis of baseline characteristics was performed. A Pearson correlation test was used to evaluate the association between the 2 definitions of BDR in CAMP. The study population was divided into a training set, consisting of a random selection of 50 cases and 50 control subjects, and a validation set, consisting of the remaining subjects, to evaluate the diagnostic accuracy of the BDR test. This allows for validation of results within our cohorts. Receiver operating characteristic curves were constructed, and areas under the curve (AUCs) were calculated for different BDR thresholds (R package pROC).[20] The AUCs for different thresholds were compared by using the DeLong test. A sensitivity analysis was performed to assess how the diagnostic accuracy of the BDR test varies across different severities of asthma. AUCs were examined for the CAMP subjects with and without evidence of baseline airflow obstruction (FEV_1 percent predicted <80% and ≥80%, respectively). *P* values are 2-sided. All analyses were performed with R software, version 2.12.1 (www.r-project.org).

RESULTS

Patient demographics

A total of 1041 children with mild-to-moderate asthma were included from the CAMP cohort (cases). Control subjects consisted of 250 children from the Project Viva and Home Allergens cohorts who had no history of wheezing and asthma at the time of the BDR test. Baseline characteristics of the study population by asthma status are presented in Table I. Although their baseline FEV_1 percent predicted values were similar and within normal limits (93.7% ± 14.3% in cases and 98.4% ± 12.2% in control subjects), the mean BDR differed between the 2 groups, as expected. Both groups consisted of predominantly white subjects. The control subjects from Project Viva were younger than those from Home Allergens (7.9 ± 0.8 vs 11.7 ± 0.5 years, respectively), but other baseline characteristics were similar, including race/ethnicity, baseline FEV_1 percent predicted, and BDR (see Table E1 in this article's Online Repository at www.jacionline.org). Baseline characteristics of subjects who performed a BDR test and those who did not are shown in