Clinical Variables Are Poor Selection Criteria for the Use of Methacholine Bronchoprovocation in Symptomatic Subjects

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OBJECTIVE: Airway hyperresponsiveness (AHR) is associated with persistent air flow limitation and accelerated FEV_1 decline. AHR can influence diagnosis, treatment, and prognosis. We assessed the value of pulmonary function variables, symptoms, and history as selection criteria for methacholine bronchoprovocation testing to detect AHR in symptomatic subjects. METHODS: Over a 4-year period we conducted a prospective study of consecutive subjects who underwent methacholine bronchoprovocation testing. Baseline pulmonary function testing (PFT) and a questionnaire were obtained prior to methacholine bronchoprovocation testing. PFT and symptom and history variables were assessed as AHR predictors in univariate and multiple logistic regression analyses for the whole group and for 4 different age groups. RESULTS: There were 530 subjects, with ages ranging from 5 to 87 years, and 232 (44%) were positive for methacholine AHR. AHR was more prevalent among subjects ≤ 25 years old (59%) and > 65 years old (47%) than among the other age groups. PFT values, symptom, and history variables had different AHR predictive values among the different age groups. Symptom and history variables had no AHR predictive value among subjects ≤ 25 or > 65 years old. CONCLUSIONS: Young and elderly symptomatic subjects are more likely to have methacholine AHR. None of the clinical variables we studied has significant predictive value for methacholine AHR across the age groups, so these variables are poor selection criteria for methacholine bronchoprovocation testing of symptomatic subjects. Given the high prevalence of AHR among these subjects, bronchoprovocation should be considered with all individuals who have respiratory symptoms of wheezing, cough, shortness of breath, or chest tightness.
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Introduction

Airway hyperresponsiveness (AHR) to various stimuli is one of the characteristics of asthma.[1] Methacholine bronchoprovocation testing is one method of assessing AHR and may be useful when asthma is suspected and spirometry is normal.[2] In addition to its association with asthma, AHR in asymptomatic subjects increases the risk of subsequent development of respiratory symptoms.[3–5] AHR is also a risk factor for persistent air flow limitation in asthma[6] and is associated with accelerated decline in forced expiratory volume during the first second (FEV_1) of exhalation from total lung capacity with subjects who do not show evidence of asthma.[7–10] Thus, detection of AHR not only assists the diagnosis of asthma but also may have implications for therapy and prognosis. Clinical predictors associated with AHR may assist in the selection of appropriate patients for bronchoprovocation testing. The presence of respiratory symptoms such as wheezing, dyspnea, chest tightness, and cough in association with certain triggers increases the probability of asthma.[11] A positive relationship between AHR and these symptoms has been demonstrated in random population samples.[12,13] However,

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the relationship between symptoms, triggers, and AHR in symptomatic subjects has not been studied. Non-airway diseases can lead to respiratory symptoms, especially in elderly patients, without any relationship to AHR. On the other hand, younger patients may be more likely to have asthma and AHR as the cause of respiratory symptoms. The presence of certain clinical predictors may therefore have different predictive value, depending on the patient's age. The purpose of the present study was to determine the prevalence of AHR in symptomatic subjects and to assess the values of pulmonary function tests (PFTs) and symptom and history variables as selection criteria for methacholine bronchoprovocation testing of subjects in various age groups.

Methods

Subjects

Consecutive patients referred to our pulmonary function laboratory for methacholine bronchoprovocation testing between May 1997 and August 2001 were recruited for the study. Patients were referred by either primary care physicians or pulmonologists in the community. All subjects had symptoms suggestive of asthma, but their histories were equivocal. Methacholine bronchoprovocation testing was ordered to confirm or exclude the asthma diagnosis. A questionnaire containing 17 questions was given to all the subjects prior to the testing. The study was approved by the Internal Review Board of the Committee for the Use of Human Subjects in Research, Memorial Hospital of Rhode Island.

Pulmonary Function Testing

Spirometry was performed using standard techniques and a commercially available spirometer (Morgan Scientific, Haverhill, Massachusetts). Following spirometry, lung volumes and specific conductance of the airways (sG_{aw}) were determined with a variable-pressure body plethysmograph (Warren E Collins Inc, Braintree, Massachusetts).[14,15] The PFT values are expressed as a percentage of predicted normal values.[16,17]

Methacholine Bronchoprovocation Testing Protocol

Methacholine bronchoprovocation testing was performed with the 5-breath dosimeter method and the United States Food and Drug Administration-approved dosing schedule of methacholine concentrations of 0.025, 0.25, 2.5, 10, and 25 mg/mL.[11] Serial dilutions of methacholine chloride (Provocholine, Methapharm, Brantford, Ontario, Canada) were prepared in normal saline containing 0.4% phenol (pH 7.0) and passed through bacteria-retentive filters with 0.2 μm porosity. Methacholine aerosol was delivered using a Rosenthal-French nebulization dosimeter (Model 2A, Laboratory for Applied Immunology Inc, Baltimore, Maryland) and a nebulizer (Model 646, DeVilbiss, Somerset, Pennsylvania) set for a 0.6 s delivery time, powered by a cylinder of compressed air, with the regulator set at 20 psi. Following a control inhalation of diluent, each patient took 5 slow inhalations from functional residual capacity (FRC) to total lung capacity from the dosimeter, starting with a methacholine concentration of 0.025 mg/mL. A forced vital capacity (FVC) maneuver was performed within 5 min of methacholine inhalation. If the reduction in FEV_1 was $< 20\%$ from baseline after 5 inhalations of 0.025 mg/mL methacholine solution, 5 inhalations of increasing methacholine concentration (0.25, 2.5, 10, and 25 mg/mL) were given. The corresponding total cumulative units (1 dose unit being 1 inhalation of 1 mg/mL) were 0.125, 1.4, 14, 64, and 189 cumulative units. The study was terminated and sG_{aw} was obtained when FEV_1 fell by $\geq 20\%$ at any concentration or when the maximum dose of methacholine (189 cumulative units) had been given. The provocative dose that caused a 20% FEV_1 decrease (PD20) was obtained by linear interpolation between points on a dose-response curve in which FEV_1 (as a percentage of the baseline value) was plotted (on the ordinate) against the log cumulative dose units (on the abscissa). Subjects with PD20 $\leq$ 100 cumulative units were considered positive for methacholine AHR.

Questionnaire Data

A questionnaire was given to all patients prior to the testing; it inquired about (1) presence of asthma symptoms and signs (wheezing, cough, shortness of breath, chest tightness); (2) frequency of symptoms (all the time, sometimes, rare); (3) presence of hay fever or allergic rhinitis; (4) presence of gastroesophageal reflux; (5) asthma triggers (environmental allergens, irritants, change in weather, exposure to cold air, exercise, emotional stress, drug, food, or other); (6) family history of asthma; and (7) current smoking status. The questionnaire was designed to simulate a physician interview of a potential asthma patient in an office setting.

Data Analysis

Subjects were divided into positive and negative groups based on PD20 (positive = PD20 $\leq$ 100 cumulative units). This cutoff value corresponded to a provocative concentration that caused a 20% FEV_1 decrease (PC20) $\leq$ 16 mg/mL. According to American Thoracic Society guidelines,[11] subjects with PC20 $>$ 16 mg/mL are considered to have normal airway responsiveness. Analyses were done for the whole group and 4 different age groups: (1) $\leq$ 25

years, (2) 26–45 years, (3) 46–65 years, and (4) > 65 years. Group mean values for all baseline pulmonary function data were calculated and expressed as mean ± SD. Differences were determined among groups by using analysis of variance and Fisher's least significant difference multiple-comparison test. Associations between individual PFT, symptom, and history variables and positive methacholine AHR were assessed by univariate logistic regression analyses. Associations were considered significant when $p < 0.05$. The analyses were then repeated for subjects in the 4 age groups to assess if the various PFT, symptom, and history variables have different predictive values in different groups. Multiple logistic regression analysis was then performed for all the significant predictors identified in the univariate logistic regression analyses for the whole group and different age groups. Variables with $p < 0.05$ were considered significant and independent predictors of methacholine AHR. The same analyses were then repeated for male and female subgroups. All analyses were performed using commercially available software (StatView, SAS Institute, Cary, North Carolina).

Results

A total of 530 subjects were included in the study. All subjects had symptoms and signs suggestive of asthma. There were 351 females (66%) and 179 males (34%). The mean age for the whole group was 41.2 ± 17.0 years. There were 100 subjects ≤ 25 years old, 227 subjects 26–45 years old, 154 subjects 46–65 years old, and 49 subjects > 65 years old. Two hundred thirty-two subjects had positive methacholine bronchoprovocation tests (44% of the total group). The proportion of subjects with methacholine AHR was highest (59%) among subjects who were ≤ 25 years old. Methacholine AHR was found in 44% of subjects 26–45 years old, 33% of those 46–65 years old, and 47% of subjects > 65 years old. Table 1 summarizes the baseline PFT data of the whole group (subjects with and without methacholine AHR). As a group, subjects with positive methacholine AHR had higher percent-of-predicted FRC and residual volume, and lower percent-of-predicted FVC, FEV_1, forced expiratory flow in the middle half of the forced vital capacity ($FEF_{25–75}$), sG_{aw}, and FEV_1/FVC at baseline. There were also significant differences between the age groups in percent-of-predicted FEV_1, $FEF_{25–75}$, sG_{aw}, and FEV_1/FVC, but not in percent-of-predicted FRC, residual volume, or FVC. In simple linear regression analyses, the coefficients of determination (r^2) were 0.04, 0.06, and 0.06, respectively, between FEV_1, FEV_1/FVC, sG_{aw}, and PD20 for the whole group with AHR (all $p < 0.005$).

Cough (76.4%) and shortness of breath (76.8%) were the most common symptoms in this subject population. About half of the subjects (50.6%) had hay fever or allergic rhinitis.

Table 1. Baseline Pulmonary Function Test Data for the Total Subject Group*

Pulmonary Function Variable	Total Subject Group (n = 530) (mean ± SD)	Positive AHR (n = 232) (mean ± SD)	Negative AHR (n = 298) (mean ± SD)
TLC (% pred.)	103.3 ± 13.7	103.9 ± 13.5	102.7 ± 13.9
FRC (% pred.)	97.3 ± 21.5	100.8 ± 22.8	94.4 ± 19.8
RV (% pred.)	99.2 ± 31.9	105.0 ± 32.2	94.3 ± 30.9
FVC (% pred.)	100.0 ± 13.5	98.2 ± 13.3	101.5 ± 13.4
FEV_1 (% pred.)	96.9 ± 14.8	92.0 ± 15.0	100.7 ± 13.4
FEV_1/FVC	80.6 ± 13.5	78.4 ± 8.2	82.2 ± 5.9
$FEF_{25–75}$ (% pred.)	89.5 ± 29.1	76.7 ± 25.9	99.4 ± 27.5
$FEV_{25–75}$/FVC	0.82 ± 0.27	0.73 ± 0.25	0.89 ± 0.26
sG_{aw} (% pred.)	95.0 ± 34.6	82.9 ± 27.5	104.4 ± 36.5

*426 subjects (80% of total subjects) had lung volume measurements. Of those 426 subjects, 194 were positive and 232 were negative for methacholine airway hyperresponsivness (AHR). For all pulmonary function variables except total lung capacity (TLC), $p < 0.05$ between the positive and negative groups.
% pred. = percent of predicted
FRC = functional residual capacity
RV = residual volume
FVC = forced vital capacity
FEV_1 = forced expiratory volume in the first second
$FEF_{25–75}$ = forced expiratory flow in the middle half of the forced vital capacity
sG_{aw} = specific conductance of the airway.

Exercise is the most commonly reported symptom trigger (61.1%), followed by irritants (57.2%) and environmental allergens (52.6%). More than half of the subjects (54.3%) reported family history of asthma and 17.0% of subjects are current smokers. When each symptom and history variable was assessed as a predictor of methacholine AHR, the presence of wheezing, cough and chest tightness, environmental allergens, change in weather, cold-air trigger, and family history of asthma were significant predictors of positive methacholine AHR for the whole group (Table 2). Among the age groups, none of the latter significant variables had significant predictive value for methacholine AHR among the youngest (≤ 25 years old) or oldest (> 65 years old) group. The prevalence of AHR was higher among females (48%) than among males (36%), but despite the difference in prevalence, similar results were obtained when the predictor data were stratified by gender.

There were 57 subjects (11%) who had baseline FEV_1 < 80% of predicted, indicating underlying airway obstruction prior to the testing. Since symptoms and history in these subjects might be due to underlying airway obstruction instead of to AHR, the analysis was repeated with only subjects whose baseline FEV_1 were ≥ 80% of predicted, of which there were a total of 473 subjects, and 185 (39%) of them had methacholine AHR. Again, young symptomatic subjects had a much higher prevalence of AHR, with 59% positivity in subjects who were ≤ 25 years old, compared to 28–38% in the other age groups. In the 473-person subgroup, subjects with positive methacholine AHR again had higher percent-

Table 2. Relative Risks and p Values of Significant Predictors for Methacholine Airway Hyperresponsiveness in Univariate and Multiple Logistic Regression Analyses for the Whole Subject Group

Predictors	Relative Risk (p)	
	Univariate Regression	Multiple Regression
PFT		
FEV_1 (% pred.)	(< 0.0001)	NS
FEV_1/FVC	(< 0.0001)	NS
$FEF_{25–75}$ (% pred.)	(< 0.0001)	(0.0003)
sG_{aw} (% pred.)	(< 0.0001)	(0.0002)
Symptoms		
Wheezing	1.8 (0.0006)	NS
Cough	1.8 (0.004)	NS
Chest tightness	1.5 (0.02)	NS
Triggers		
Environmental allergens	1.9 (0.0005)	NS
Change in weather	1.7 (0.004)	NS
Cold air	1.7 (0.004)	NS
Family history	1.6 (0.009)	NS

PFT = pulmonary function test
NS = not significant
FEV_1 = forced expiratory volume in the first second
% pred. = percent of predicted
FVC = forced vital capacity
sG_{aw} = specific conductance of the airways

of-predicted FRC and residual volume, and lower percent-of-predicted FEV_1, $FEF_{25–75}$, sG_{aw}, and FEV_1/FVC. The same symptom and history variables (wheezing, cough, chest tightness, environmental allergens, change in weather, cold air and family history) were also significant predictors for methacholine AHR for the 473-person subgroup. But, again, none of these symptom and history variables had significant predictive values in the youngest and oldest groups.

Multiple logistic regression analysis was performed to include all the PFT, symptom, and history predictors that were significantly associated with positive methacholine AHR in univariate logistic regression analyses, and only baseline percent-of-predicted $FEF_{25–75}$ and sG_{aw} were significantly and independently associated with positive methacholine AHR for the whole group (see Table 2). When the same analysis was performed for the age groups, different predictors had different predictive values for methacholine bronchoprovocation outcome. Among subjects ≤ 25 years old, none of the PFT, symptoms, or history data could predict positive methacholine AHR. For subjects 26–45 years old, environmental allergen(s) as symptom trigger(s) was the only significant predictor (relative risk 2.4, $p = 0.01$). For subjects 46–65 years old, percent-of-predicted $FEF_{25–75}$ ($p = 0.003$), cold air as a symptom trigger (relative risk 3.2, $p = 0.02$), and positive family history of asthma (relative risk 3.5, $p = 0.005$) were significant and independent predictors. For subjects > 65 years old, percent-of-predicted FEV_1 was the only significant predictor of positive methacholine AHR ($p = 0.04$). The results were similar when subjects with baseline FEV_1 < 80% of predicted were excluded from these analyses. When the analysis was repeated for male and female subgroups, similar results were again obtained, with none of the predictors having significant association with methacholine AHR in 3 out of the 4 age groups (≤ 25 years old, 26–45 years old, and > 65 years old) in either male or female subgroups.

Discussion

This study demonstrates that certain baseline PFT, symptom, and history variables are, statistically, predictors of methacholine AHR in symptomatic subjects, but the variables have different predictive values for different age groups. None of the clinical predictors has significant predictive value across the age groups. Symptoms and history are particularly poor predictors of methacholine AHR in the youngest and oldest groups.

AHR is a common feature of asthma. Bronchoprovocation testing as a method to assess AHR could be useful in the diagnosis of asthma when the history is suggestive but the spirometry is normal.[2] However, despite its diagnostic value for asthma, the best way to use bronchoprovocation remains controversial, because AHR is characteristic of, but not specific for, asthma. AHR is encountered in other airway diseases, such as chronic obstructive pulmonary disease,[18,19] and in asymptomatic individuals.[20–22] The clinical importance of AHR in asymptomatic subjects is unclear, but AHR increases the risk of subsequent development of respiratory symptoms.[3–5] It is possible that bronchoprovocation might have a role in screening for subjects at risk of asthma before they become symptomatic. Further larger-scale studies will be necessary to answer that question. AHR is also associated with accelerated decline in lung function.[7–10] These findings suggest the need for intervention trials to determine whether therapies that reduce nonspecific AHR can slow the progression of chronic air flow obstruction.[8] The presence of AHR, as detected by bronchoprovocation, therefore not only assists in diagnosing asthma, it may also have prognostic implications and help in identifying high-risk subjects.

The prevalence of AHR in the general population is probably around 14–16%.[21–23] The determinants of AHR have been reported in random population samples.[12,13] In a study of 1,905 subjects from the Netherlands, Rijcken et al reported a statistically significant relationship between AHR and respiratory symptoms and signs, including wheezing, dyspnea, and chronic cough.[12] In a study of 875 young adults in Italy, airway caliber represented by FEV_1 and asthma symptoms were independent predictors of AHR.[13] In studies of selected populations, such as grain handlers[24] and insulators,[25] respiratory symptoms were also associated with AHR. It appears from those studies that various respiratory symptoms predict

AHR. The AHR prediction value of various clinical and history variables in symptomatic subjects is expected to be different than the general population, but data on this are limited. If positive clinical predictors of AHR can be identified in symptomatic subjects, those predictors may be used as selection criteria for bronchoprovocation tests.

All the subjects in the present study were symptomatic, each with at least one of: wheezing, cough, shortness of breath, and/or chest tightness. Although our study population may be biased because we cannot claim to have included all the symptomatic subjects in the area, the AHR positivity in our study (44%) is in the same range as a study of 791 symptomatic patients referred to a pulmonary clinic in Finland (50%).[26] The higher prevalence in the Finnish study might be due to inclusion of patients with chronic bronchitis and lower baseline FEV_1 (mean percent-of-predicted FEV_1 88.9 ± 15.8%). Since our subjects were referred by physicians in the community, one potential bias in our study might be that these subjects were more likely to have AHR than subjects from a general population, in which case the symptom and history variables would be stronger predictors in this group than in a general population. But since our results showed that these variables were weak predictors in this group of subjects, the selection bias would not have affected the outcome of the present study.

In our group of symptomatic subjects, lower baseline percent-of-predicted FEV_1, $FEF_{25–75}$, sG_{aw}, and FEV_1/FVC were all associated with positive methacholine AHR. The higher prevalence of AHR in subjects with lower baseline percent-of-predicted FEV_1 and FEV_1/FVC have been well documented in population-based studies[13,24,27] and among patients with chronic obstructive pulmonary disease.[18,19] Our results agree with those previous studies. Since FEV_1, $FEF_{25–75}$, and sG_{aw} are surrogates for airway diameter, our results also confirm the relationship between small airway diameter and AHR.

The presence of wheezing, cough, and chest tightness are also associated with AHR. However, the relative risk of AHR with the presence of an individual symptom is low (relative risk 1.5–1.8). AHR predictors include family history of asthma and symptom triggers such as environmental allergens, changes in weather, and exposure to cold air, but the relative risk with these variables is also low (relative risk 1.6–1.9). In a multiple regression model of all these predictors, only the baseline percent-of-predicted $FEF_{25–75}$ and sG_{aw} retained independent predictive value. These findings demonstrate that symptoms and history are poor AHR predictors with symptomatic subjects and that the baseline percent-of-predicted $FEF_{25–75}$ and sG_{aw} (but not FEV_1) are independent predictors of AHR in symptomatic subjects. Baseline airway caliber, as reflected by FEV_1, is a factor in AHR.[24,28–30] Since the majority of our subjects had normal baseline FEV_1, our results may reflect the higher sensitivity of $FEF_{25–75}$ and sG_{aw} in detecting small changes of airway caliber.

Age appears to have an effect on AHR. Weiss et al[21] studied AHR in a random sample of 134 adults and 213 children in Boston, using the technique of eucapnic hyperventilation of cold air. They found that AHR was most frequent in subjects between the ages of 5 and 24 years, and the frequency decreased with increasing age, up to 58 years old. However, a study of 1,905 randomly selected Dutch subjects, ages 14–64 years, showed a progressive increase in AHR to histamine with increasing age.[12] In another population-based study, Burney et al[23] found a U-shaped distribution of histamine AHR by age among 511 subjects, ages 18–64 years. The prevalence was highest among the 18–24-year-old subjects, less among those ages 35–44 years, and then higher in the 55–64-year age group. The differences in results might be due to the different methods of testing and threshold of AHR.

The prevalence of AHR in symptomatic subjects of different age groups is less well known. In our subject population the highest prevalence of methacholine AHR was among symptomatic subjects ≤ 25 years of age. Subjects > 65 years old had the second-highest prevalence of methacholine AHR. It appears that methacholine AHR also has a U-shaped distribution by age among symptomatic subjects, similar to the distribution in the general population reported by Burney et al.[23]

Since similar respiratory symptoms may be caused by nonairway diseases, such as heart disease, which have different prevalences in different age groups, it is possible that different clinical predictors have different predictive values in different age groups. None of the significant clinical predictors of methacholine AHR for the whole group had any predictive value among subjects ≤ 25 years of age. Clinical predictors have similar poor predictive values among elderly subjects, except for percent-of-predicted FEV_1, a low value of which is associated with AHR in this age group. For symptomatic subjects ages 26–65 years certain clinical variables are associated with AHR, but none of the variables has significant predictive value across the age groups.

Bronchoprovocation testing is the method most commonly used to document AHR, but it is well known that many factors affect the presence and degree of AHR in an individual at any given time. Recent symptoms increase the pre-test probability of AHR, and the intrasubject reproducibility may diminish beyond 8 weeks.[11] Since symptoms associated with AHR or any obstructive airway disease tend to be intermittent, it is important to perform the bronchoprovocation testing in a timely fashion to maximize its clinical utility.

Conclusions

We conclude that the presence of any of the respiratory symptoms of wheezing, cough, shortness of breath, and/or chest tightness is associated with AHR, since nearly half of symptomatic subjects will have positive response to bronchoprovocation. AHR has a U-shaped age distribution in symptomatic subjects. Individual symptoms, history,

and baseline PFT data have limited value in predicting the presence of AHR and are therefore poor selection criteria for bronchoprovocation testing in symptomatic subjects. Since AHR has a high prevalence in symptomatic subjects and is associated with accelerated decline in pulmonary function, bronchoprovocation should be considered in subjects with any of the respiratory symptoms/signs of wheezing, cough, shortness of breath, and/or chest tightness, especially if they are < 25 or > 65 years of age.

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