Published in final edited form as:

Clin Exp Allergy. 2011 January ; 41(1): 46–51. doi:10.1111/j.1365-2222.2010.03627.x.

Negative methacholine challenge tests in subjects who report physician-diagnosed asthma

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Abstract

Background—The frequency of adults reporting a history of asthma is rising. However, it is unclear whether this increased prevalence accurately demonstrates a rising trend or if it reflects an overall increase in asthma awareness.

Objective—To determine the frequency of negative methacholine bronchoprovocation tests in adults who report physician-diagnosed asthma and to explore the clinical characteristics of subjects with negative tests.

Methods—Data from methacholine challenge, spirometry, and physician assessment were analysed from 304 adults who reported physician-diagnosed asthma and responded to community based advertising for asthma research studies. The clinical characteristics of methacholine-positive and -negative subjects were compared and a predictive model was tested to identify those characteristics associated with a negative test.

Results—Of the 304 subjects tested, 83 (27%) had a negative methacholine test. A negative test was positively associated with adult-onset of symptoms ($p < 0.001$), normal FEV₁ ($p < 0.001$), and having no history of exacerbation requiring oral steroids ($p = 0.03$). Over half (60%) of those with a negative test reported weekly asthma-like symptoms (cough, dyspnea, chest tightness or wheeze), while 39% reported emergency department visits for asthma-like symptoms.

Conclusions and Clinical Relevance—A sizeable percentage of subjects who report physician diagnosed asthma have a negative methacholine challenge test. These subjects are characterized by diagnosis of asthma as an adult and by normal or near normal spirometry. Caution should be exercised in the assessment and diagnosis of adults presenting with asthma-like symptoms, because they may not have asthma. Further diagnostic studies, including bronchoprovocation testing, are warranted in this patient group, especially if their spirometry is normal. (ClinicalTrials.gov - NCT00201266).

Keywords

Asthma; Diagnosis and Assessment; Brochoprovocation Testing

INTRODUCTION

The estimated frequency of adults reporting a history of asthma in the U.S. rose from 2.9% in 1980 to 6.7% in 2003 [1]. However, the degree to which this increased prevalence is skewed by an overall increase in asthma awareness remains unclear. With the dissemination of national asthma guidelines within the medical community and the direct-to-consumer

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Declaration of Interest: Ms. Wong McGrath and Dr Fahy report no conflicts of interest, financial or otherwise. Ms. Wong McGrath and Dr Fahy alone are responsible for the content and writing of the paper.

marketing of asthma medications, a heightened awareness of asthma has developed on both sides of the patient-clinician relationship. This increased consciousness has resulted in a tendency towards branding any persistent cough, wheeze, or dyspnea as asthma [2].

Understanding the interplay of how prevalence has been influenced by heightened awareness is complicated by the lack of a single method by which to diagnosis asthma with certainty. National guidelines recommend assessment based on the patient's medical history, and physical examination combined with spirometric evidence of reversible airway obstruction to establish a diagnosis [3]. While spirometry is typically chosen for its relative technical ease and minimal expense, a normal result cannot exclude asthma and incorrect interpretation of results can lead to misdiagnosis [4].

Bronchoprovocation with methacholine is a particularly sensitive diagnostic tool and can be used to exclude a diagnosis of asthma. A provocative concentration of methacholine causing a $\geq 20\%$ fall in FEV_1 (PC_{20}) of greater than 16mg/mL excludes airway hyperresponsiveness [5]. A positive PC_{20} , when combined with the patient's medical history and physical examination, can help to establish a conclusive asthma diagnosis. However, bronchoprovocation testing is more costly and requires greater technical skill than basic spirometry, making it a less favorable diagnostic study.

We conducted this study to determine the frequency of a negative methacholine challenge test in a community-based sample of adults with physician-diagnosed asthma. Our goal was to identify the size and clinical characteristics of this subgroup.

METHODS AND MATERIALS

Subjects

We analysed data for 304 subjects who had been recruited for a larger observational study on molecular phenotypes of asthma (NCT00201266). Subjects had been recruited from the community and asked to participate if they had a history of physician-diagnosed asthma. Subjects included had been current nonsmokers with less than 10 pack-years of smoking history, aged 18 to 73 years with a positive PC_{20} or spirometric evidence of reversible airflow obstruction. A PC_{20} was considered positive if the concentration of methacholine causing a 20% fall in FEV_1 was less than 16mg/mL in subjects on an inhaled corticosteroid (ICS) and less than 8mg/mL in subjects not on an ICS. The higher limit was chosen for those subjects on an ICS, because corticosteroids can lessen sensitivity to methacholine [6]. Exclusion criteria included history of concurrent lung disease other than asthma, history of significant cardiac disease, or current pregnancy. The study was approved by the Institutional Review Board, and all subjects gave informed consent.

Subjects included in the analysis reported here were limited to those who either (1) had a positive PC_{20} and were subsequently enrolled in the original study or (2) had a negative PC_{20} and were subsequently excluded from the original study. Subjects were excluded from this new analysis if they (1) did not undergo methacholine challenge, due to severe baseline airflow obstruction ($FEV_1 < 50\%$ predicted), (2) were excluded from the original study for reasons other than negative PC_{20} , or (3) had been unable to hold long-acting beta agonist (LABA) for 48 hours and/or short-acting beta-agonist (SABA) for 8 hours prior to methacholine challenge. All subjects included in the analysis reported here had a complete medical history and physical examination by a physician, in addition to baseline spirometry and methacholine challenge. All subjects also had completed a self-administered asthma characterization questionnaire.

Baseline Spirometry & Methacholine Challenge

After holding LABA for 48 hours and SABA for 8 hours, subjects underwent baseline spirometry according to the American Thoracic Society guidelines [7]. Subjects with a baseline $FEV_1 \geq 50\%$ predicted then underwent methacholine challenge in accordance with American Thoracic Society standards [5]. Methacholine challenge was performed using a five breath dosimeter method [8]. Methacholine chloride powder (Methapharm, Brantford, Ontario, CN) was diluted in sterile 0.9% sodium chloride (Abbott Laboratories, North Chicago, IL) and delivered using a dosimeter device (Micro-Dosimeter, S&M Instrument Company, Doylestown, PA). Subjects inhaled aerosolized normal saline, followed by aerosolized saline containing methacholine in doubling doses from 0.03 to either 8.0mg/mL or 16.0mg/mL (depending on ICS use/nonuse). At each interval, subjects took five inhalations from functional residual capacity to total lung capacity while wearing a nose clip. Three FEV_1 maneuvers were measured 2.5 minutes after each dose interval; doubling doses were administered in this manner until either FEV_1 fell by 20% of baseline or until the final dose was administered. If a subject experienced a drop in FEV_1 from baseline of greater than or equal to 20% before or immediately after the administration of the final dose, the test was considered positive; inability to achieve a 20% fall or greater in FEV_1 by the final dose the test was considered negative.

Statistical analysis

Subjects were categorized as having either a positive or negative PC_{20} and compared by demographic and clinical characteristics. To test significance, we used Student's t test for continuous variables and continuity adjusted X^2 test for categorical variables. Potential predictors of negative PC_{20} were selected for multiple logistic regression analysis if the groups differed in the bivariate analysis at a significance level of $p \leq 0.10$. When predictors were highly correlated, we selected only one for entry into the logistic regression. All statistical analyses were conducted using SPSS version 15.0 (SPSS, Inc. Chicago, IL).

RESULTS

We found that methacholine PC_{20} was negative in 83 of the 304 subjects (27%) who report a history of physician diagnosed asthma. Of the subjects with a negative PC_{20} , 82% were not taking an ICS and the negative result was determined with a methacholine dose of 8 mg/mL; a minority of subjects (18%) were taking an ICS and a negative PC_{20} was determined with a dose of 16mg/mL. Of the 221 subjects with a positive PC_{20} , 64% had a positive result with a methacholine dose ≤ 1 mg/mL, 29% had a positive result with ≤ 4 mg/mL, and only 7% required a dose between 4 - 16 mg/mL to determine a positive result.

The subgroup of subjects with negative PC_{20} did not differ from the subgroup with a positive test with respect to gender, race, body mass index, smoking history, or atopy, but multiple other differences were apparent (Table 1). Specifically, subjects with a negative PC_{20} were significantly older and more frequently had asthma diagnosed as an adult. Additionally, these subjects tended to have better spirometry values. For example, the proportion of subjects with normal or near-normal lung function in the subgroup with a negative PC_{20} test was significantly greater than in the subgroup with a positive test (Table 1), and evidence for airflow limitation was lacking or mild in this subgroup (only 11% had an FEV_1/FVC ratio $<70\%$ and 34% had $FEF_{25-75} <70\%$).

The ratio of FEF_{25-75} to FVC is used as a surrogate measure of dysanapsis (a term used to describe disproportionate airway growth compared to lung parenchyma growth.). We found that the FEF_{25-75} to FVC ratio was significantly lower in the methacholine positive group than in the methacholine negative group (Table 1), but the overall relationship between

FEF₂₅₋₇₅/FVC and methacholine reactivity was relatively weak, with FEF₂₅₋₇₅/FVC values accounting for just 6.2% of variability in airway reactivity.

Despite the frequency of near-normal lung function, the subjects with a negative methacholine challenge test reported significant morbidity ascribable to airway disease. For example, 60% reported weekly asthma-like symptoms (cough, dyspnea, chest tightness or wheeze) when questioned by a physician, 48% reported weekly use of albuterol, and 18% had a current prescription for an ICS and were actively using it. In addition, self-report of asthma-related healthcare utilization was not trivial in this subgroup; 39% reported lifetime history of an emergency department visit for asthma-like symptoms, with 13% reporting related hospitalization and 3% reporting related intubation. Close to a third (28%) had been prescribed oral steroids for an exacerbation of asthma-like symptoms in the previous 2 years.

Based on the above findings, we tested a bivariate predictive model of negative PC₂₀. The multiple logistic regression analysis included the following variables: adult onset, normal lung function (FEV₁ ≥90% predicted), and no history of exacerbation requiring oral steroids. Age was dropped from the model for high correlation with the adult onset variable. Normal lung function was chosen as the stand-in variable for other lung function perimeters because of its clinical relevance and translatability. The overall model was significant (X² likelihood ratio 55.27, *df*=3, *P*<0.001)(Table 2). A diagnosis of adult onset asthma (≥18 years) was a significant predictor of negative PC₂₀, as was normal lung function and absence of a history of asthma exacerbation requiring treatment with oral steroids (Table 2). To further validate our findings, we replicated the model with only those subjects not taking an ICS. The results were similar in that the model was significant; adult-onset asthma (OR 2.64, CI 1.40-4.95, *p*=0.004) and FEV₁ ≥90% predicted (OR 2.81, CI 1.47-5.35, *p*=0.002) remained significant predictors of negative PC₂₀. While we chose to keep the lack of oral corticosteroids in the previous 2 years as a potential predictor of negative PC₂₀ in the model for consistency, it was not, nor did we expect it to be, a significant predictor, given that oral corticosteroid use for an asthma exacerbation without a concomitant ICS prescription is not standard of care.

DISCUSSION

In a sample of over 300 subjects who report a history of physician-diagnosed asthma recruited directly from the community, we found that 27% had a negative methacholine challenge test, a negative test frequency that is within the 25-40% range noted by others [6,9]. Compared to the methacholine positive subgroup, the clinical characteristics of the methacholine negative subgroup included an older age of asthma onset and better lung function.

One interpretation of our data is that the methacholine negative subgroup had false negative results. For example, methacholine challenge is acknowledged as a highly sensitive test for asthma, but it can be negative in subjects who are not having active symptoms, in subjects who have normal lung function, or in elite athletes with exercise-induced asthma [10-12]. In particular, it is well recognized that athletes with good lung function can have exercise-induced asthma and negative methacholine tests [13]. Although the subgroup here with a negative methacholine challenge test was characterized by well-preserved lung function, they were not characterized as having asthma in remission, because their histories revealed significant symptoms and health care utilization. In addition, methacholine challenge sensitivity can be reduced by using forced maneuvers to measure airflow (as we did), since the deep breath can reverse bronchoconstriction [14-15]. It is possible, therefore, that subjects with negative methacholine challenge in our study could have had a positive test

result using a different methacholine protocol or that they could have had a positive result with an indirect bronchoprovocation challenge with exercise, eucapnic voluntary hyperpnea, or adenosine monophosphate. It is also possible that adult onset asthma is characterized by lack of methacholine responsiveness; certainly, children (who also have short asthma durations) can have normal lung function, have exercise induced bronchospasm, and yet have negative methacholine tests [10-11]. All of these possibilities mean that it is not possible to fully exclude a false negative result for asthma in the subgroup identified here as methacholine negative. It has recently been reported that methacholine challenge testing does not have a high negative predictive value for a clinical diagnosis of asthma [12]. The study on which this conclusion was based required subjects to have signs and symptoms suggestive of asthma but no firm diagnosis of asthma. These unusual entry criteria were necessary to optimize the protocol to determine the usefulness of mannitol as a bronchoprovocation test in this kind of patient population. Only 42% of the enrolled subjects were positive for methacholine, a percentage far lower than in other studies that had less unusual enrollment criteria. In addition, the average FEV₁ was over 90% and less than 10% of subjects had beta-agonist reversibility. So although clinicians thought it likely that these subjects had asthma, the normal lung function and normal methacholine results suggest some of the clinician-based diagnoses of asthma were incorrect and that the negative methacholine test was a true negative for the diagnosis of asthma.

Although we acknowledge the possibility of a false negative methacholine test for the diagnosis of asthma in a subgroup of our study population, we consider it very likely that a large fraction of the negative methacholine subgroup did not have asthma. This interpretation is based on the findings that the methacholine negative subgroup were characterized by a high frequency of asthma diagnosis as an adult and by normal or near normal spirometry. As discussed above, it is possible that adult onset asthma is a peculiar asthma phenotype that is less likely to be characterized by methacholine responsiveness. But we consider it more likely that adult onset asthma is a subgroup more likely to be misdiagnosed. Similarly, although spirometry can be normal in stable asthma (and it was indeed normal in over one third of subjects in the methacholine positive subgroup), and methacholine challenge tests are more likely to be negative when lung function is normal [16], the fact that 72% of the methacholine negative subgroup had normal spirometry is unusual and suggests an incorrect diagnosis of asthma in many of these subjects.

Dysanapsis is a term used to describe disproportionate airway growth compared to lung parenchyma growth and dysanapsis has been proposed as a determinant of bronchial hyperresponsiveness [17-19]. Since direct measures of airway and lung size are not feasible *in vivo*, the ratio of FEF₂₅₋₇₅ to FVC is used as a surrogate [20]. Although a low ratio is known to predict airway hyperresponsiveness [18-19], it is not the main determinant, accounting for just 7.6% of variability in airway reactivity in a previous study of 764 pediatric and adult subjects presenting to a clinical pulmonary function laboratory for methacholine testing [19]. We found a similar finding here - the FEF₂₅₋₇₅ to FVC ratio was significantly lower in the methacholine positive group than in the methacholine negative group but the overall relationship between FEF₂₅₋₇₅/FVC and methacholine reactivity was relatively weak.

Much of the literature focuses on missed opportunities to diagnosis and treat asthma, with little research devoted to indentifying reasons for over-diagnosis of asthma [21-22]. This may be contributing to a trend towards diagnosing any persistent cough, wheeze, or dyspnea as asthma, in an effort to err on the side of caution. There is evidence that the diagnosis of asthma is often made in absence of any diagnostic studies. A Swedish study recently reported that of 499 individuals with a confirmed diagnosis of asthma, only 20% had ever received spirometric assessment [23].

There was significant morbidity referable to airway disease in the subjects with a negative methacholine test. Many had airway symptoms and reported regular use of albuterol or ICS. More impressively, some reported emergency department visits or hospitalizations and close to a third had been prescribed oral steroids for an exacerbation of asthma-like symptoms in the previous 2 years. It is possible that the subjects with the emergency room visits and hospitalizations represent the fraction of the methacholine negative subgroup that indeed had asthma. It is also possible, however, that non-asthmatic airway disease due to vocal cord dysfunction or to viral or bacterial bronchitis was the correct diagnosis in these patients.

Our study had several limitations. For example, while participants had to have a physician-diagnosis of asthma, this inclusion criterion was by self-report. We were not able to verify physician-diagnosis against the patient's medical record nor were we able to determine the method by which the physician made the diagnosis. This could have allowed some subjects into the study who may have either received an unfounded diagnosis, or who may have incorrectly recalled a positive diagnosis of asthma. In addition, subjects were asked to hold SABA and LABA before methacholine testing, but they were not asked to hold ICS except when in combination preparations with LABA. There is some research to suggest that asthmatics with negative PC₂₀ can have a positive PC₂₀ when retested after holding ICS for 2-3 weeks [6]. While this is not a consistent finding across the literature [24], it is possible that not asking subjects to hold ICS could have inappropriately categorized some individuals, who may have otherwise had a positive PC₂₀. Given that 82% of the subjects with a negative PC₂₀ were not prescribed an ICS and that the remaining 18% were tested using a higher PC₂₀ threshold, it is only a small fraction of subjects who could have been vulnerable to this type of misclassification. Even so, adult onset asthma and FEV₁ ≥90% predicted remained significant predictors of negative PC₂₀ when the model was restricted to steroid naïve subjects; further strengthening the validity of our findings. Using a PC₂₀ of 8mg/mL as the cutoff for subjects not on ICS may have been a limiting factor in this study. ATS guidelines suggest that a PC₂₀ between 4mg/mL and 16mg/mL indicates borderline airway hyperresponsiveness, whereas a PC₂₀ less than 4mg/mL is evidence of airway hyperresponsiveness [5]. Thus, there is a possibility that subjects with a negative PC₂₀ would have subsequently had a positive PC₂₀ if the 16mg/mL threshold was used for all subjects. However, the vast majority of those with a positive PC₂₀ reacted to methacholine at or below the 4mg/mL dose, before the 8mg/mL cutoff was reached.

Clinical Significance

In a review of methacholine challenge tests in a large group of subjects who report physician-diagnosed asthma, we find a sizeable percentage with negative tests. These subjects are characterized by a diagnosis of adult-onset asthma and by normal or near normal spirometry. Based on these findings, we urge caution in the assessment and diagnosis of adults presenting with asthma-like symptoms, because they may not have asthma. Methacholine bronchoprovocation testing should be considered in this patient subgroup, especially if their spirometry is normal.

Inappropriately diagnosing individuals with asthma is not without consequences. Those individuals with an improper diagnosis are burdened with the cost and exposed to the side effects of medications they may not need. Providing asthma-related care to individuals who do not have asthma is a misuse of resources and diminishes the opportunity to examine the underlying pathology behind the individual's asthma-like symptoms, which may increase future risk associated with untreated disease. In addition to the implications for individual patient outcomes, misdiagnosing asthma has considerable implications on the validity and reliability of asthma research.

Acknowledgments

JV Fahy designed the study. KW McGrath wrote the analysis plan with JV Fahy; KW McGrath did the analyses. Both authors contributed to the interpretation of the data and the writing of the manuscript. We thank site investigators, Drs Anh Innes and Ryan Dougherty, and site coordinators, Ms. Kimberly Okamoto, Ms. Kelsey Ingmundson and Mr. Jack Covington, for their collaboration.

Declaration of Support: This work was supported by the National Institutes of Health [Grants U19 A1077439, R01 HL080414].

ABBREVIATIONS

FEV₁	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
FEF₂₅₋₇₅	Forced Expiratory Flow from 25% to 75% (aka Maximal Mid-Expiratory Flow)
ICS	Inhaled Corticosteroids
SABA	Short-Acting Bronchodilator
LABA	Long-Acting Bronchodilator
PC₂₀	Provocative Concentration of Methacholine Causing a $\geq 20\%$ Fall in FEV ₁

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Table 1

Clinical characteristics of study participants by methacholine challenge test outcome

Characteristic	Positive PC ₂₀ n=221	Negative PC ₂₀ n=83	p
	N (%) or Mean ± SD		
Age	34.8 ± 12.8	38.3 ± 13.0	0.04
Female gender	151 (68)	63 (76)	0.25
Race			
Asian	33 (15)	14 (17)	0.25
Black/African-American	34 (15)	6 (7)	
Caucasian, Non-Hispanic	120 (54)	46 (55)	
Caucasian, Hispanic	34 (15)	17 (21)	
Height (cm)	168.3 ± 9.3	167.7 ± 8.2	0.40
Weight (kg)	81.7 ± 23.2	82.8 ± 27.8	0.75
Body Mass Index	28.9 ± 8.3	29.6 ± 9.5	0.49
Adult-onset asthma (≥ age 18)	58 (28)	39 (51)	<0.001
Lung Function Parameters			
FEV ₁ % Predicted	85.3 ± 14.5	96.2 ± 12.4	<0.001
FVC % Predicted	96.7 ± 13.8	99.2 ± 12.8	0.16
FEV ₁ to FVC Ratio	73.3 ± 10.0	80.0 ± 8.4	<0.001
FEF ₂₅₋₇₅ to FVC Ratio	54.1 ± 1.6	70.5 ± 2.7	<0.001
FEF ₂₅₋₇₅ % Predicted	59.5 ± 23.3	81.2 ± 24.4	<0.001
Normal lung function (FEV ₁ ≥90%)	78 (35)	60 (72)	<0.001
FEV ₁ /FVC ratio <70% predicted	76 (34)	9 (11)	<0.001
FEF ₂₅₋₇₅ <70% predicted	152 (69)	28 (34)	<0.001
Smoking history*			
Never	84 (38)	34 (43)	0.24
Less than 1 pack-year	84 (38)	23 (29)	
1 -10 pack-years	53 (24)	22 (28)	
Weekly albuterol use	158 (71)	40 (48)	<0.001
Weekly symptoms	172 (78)	50 (60)	0.12
Prescribed an inhaled corticosteroid	107 (48)	15 (18)	<0.001
No history of exacerbation requiring oral steroids	118 (55)	57 (71)	0.02

Characteristic	Positive PC ₂₀ n=221	Negative PC ₂₀ n=83	p
	N (%) or Mean ± SD		
History of allergies	195 (89)	54 (84)	0.33
History of wheeze with exercise	163 (74)	51 (61)	0.13
History of asthma-related care:			
Emergency Department visit	138 (62)	30 (39)	<0.001
Hospitalization	59 (27)	10 (13)	0.007
Intubation	13 (6)	2 (3)	0.20
Oral steroids use in previous 2 years	99 (45)	23 (28)	0.006

* Detailed smoking history is unavailable for 4 subjects in the negative PC₂₀ group.

Table 2

Logistic regression model for predictors of misdiagnosed asthma (n=83)

Outcomes and Interactions	OR	95% Confidence Interval		p
		Lower	Upper	
Adult-onset asthma ($\geq$ age 18)	3.10	1.69	5.70	<0.001
FEV ₁ $\geq$ 90% predicted	5.22	2.81	9.73	<0.001
No history of exacerbation requiring oral steroids	0.52	1.05	3.74	0.03

Note Overall model X^2 likelihood ratio 55.27, $df=3$, $P<0.001$.