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Prognostic value of methacholine challenge in patients with respiratory symptoms

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Abstract

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Background: The objective was to study the current clinical status of 78 adults with respiratory symptoms, who were referred 3 to 10 years ago for diagnostic methacholine challenge. We tested the hypothesis that methacholine hyperresponsiveness would be associated on follow-up with increased symptoms of chest tightness, dyspnea, wheezing, cough, and more frequent use of selected treatment modalities.

Methods: Current symptoms were evaluated by means of interview questionnaire, and methacholine

challenge was repeated during follow-up examination. Comparisons were made between patients who were and those who were not hyperresponsive to methacholine at initial and follow-up challenges by using specific symptoms and calculated symptom and treatment scores.

Results: We found that subjects who had positive methacholine challenge results on initial challenge ($n = 37$) were significantly more likely than those with negative results ($n = 41$) to have nonexertional chest tightness, wheezing, and dyspnea, but not cough. A high proportion of both groups had current symptoms. Two thirds of the patients continued to have positive ($n = 25$) or negative ($n = 27$) methacholine challenge results, and one third had a change in status ($n = 26$). Significant correlations were also found between follow-up methacholine responsiveness and concurrent symptoms, again with the exception of cough.

Conclusions: Methacholine challenge warrants cautious interpretation in the individual patient as an aid to diagnosis and prognosis in the evaluation of respiratory symptoms, especially cough. (J ALLERGY CLIN IMMUNOL 1994;94:77-87.)

CBU Cumulative breath units (1 breath unit = 1 breath of 1 mg/ml of methacholine)

FEV₁ Forced expiratory volume in 1 second

FVC Forced vital capacity

MCh Methacholine challenge

PD₂₀ Provocative dose causing a 20% fall in FEV₁

(Click on a term to search this journal for other articles containing that term.)

Key words: [Asthma](#), [methacholine](#), [bronchoprovocation](#), [hyperresponsiveness](#), [tightness](#), [wheezing](#), [dyspnea](#), [cough](#), [prognosis](#)

Nonspecific bronchial hyperresponsiveness can be measured with the use of hyperventilation, exercise, or various inhaled agents such as methacholine, histamine, prostaglandin F_{2α}, and carbachol.¹ The use of methacholine inhalational challenge (MCh) has become widely accepted as a clinical tool to evaluate patients who are first seen with respiratory symptoms suggestive of asthma.² Asthma is associated with bronchial hyperresponsiveness that is characterized by wide variations in resistance to flow within intrapulmonary airways over short periods of time; clinical symptoms of chest tightness, cough, wheezing, and dyspnea often occur at night and are typically not limited to effort.^{3 5} These criteria are frequently difficult to document, and asthma may be diagnosed in patients with suggestive symptoms, normal spirometry results, and positive MCh results. To what extent airway hyperresponsiveness to methacholine is predictive of the future course of symptoms in such patients is uncertain.

We set out to re-administer methacholine to a group of 78 adults who had initially been referred for diagnostic methacholine challenge 3 to 10 years earlier to help the referring physician evaluate respiratory symptoms suggestive of asthma. Through the use of an interview questionnaire, at the time of the follow-up evaluation, information was gathered about the subjects' current respiratory symptoms and medications, and symptom and treatment scores were calculated for each individual.

The study was designed to test a hypothesis that subjects with symptoms who had initially positive MCh results would, on follow-up, have more chest tightness, shortness of breath, wheezing, and cough especially — at rest or at night — and that they would be using more antiasthma medications. We were thus able to test the value of MCh responsiveness in predicting the clinical status 3 to 10 years later. Our intent was not to establish or refute a diagnostic label for these subjects but to determine to what extent the presence or absence of nonspecific airway hyperresponsiveness was related to the future symptomatic course. We also evaluated the present status of methacholine responsiveness and its association with concurrent symptoms and therapy.

Methods

TOP

Study design

Patient population

During the years 1978 through 1988, 361 patients were referred from services within the Internal Medicine Department to the Allergy-Immunology Laboratory for MCh testing. The group consisted of adults with respiratory symptoms of varying severity in whom the results of spirometry were not definitive and the diagnosis of asthma was entertained but not established. In 1990, these patients were contacted by a questionnaire sent to the last mailing address on record, and subsequent telephone calls were made in an attempt to trace those who failed to return the questionnaire.

The questionnaire concerned current diagnosis and ongoing symptoms and treatment and was based on the American Thoracic Society Epidemiological Standardization Project⁶ and the International Union Against Tuberculosis and Lung Disease Bronchial Symptoms Questionnaire.⁷ The return rate was 58%. Missing returns were attributable almost exclusively to moves without forwarding addresses. Results of the mailed questionnaire were reported in abstract form.⁸

Study subjects

One hundred ninety-seven patients were contacted by telephone in 1991 and invited to participate in this study. Study protocols were approved by the University of Iowa Institutional Review Board for Human Studies, and informed consent was obtained from all subjects enrolled in the study. Seventy-eight patients agreed to participate in repeat MCh and interview history. A study nurse, unbiased by previous questionnaire results, submitted the questionnaire to the subjects in the form of an interview before the follow-up MCh. The primary purpose of the interview questionnaire was to obtain accurate information on each subject's current symptomatic and treatment status. A physical examination and a baseline pulmonary function test preceded the challenge. The patients' earlier medical records were reviewed to document indications for the initial MCh. All of the other symptom and treatment data evaluated in this report refer to information obtained from the follow-up interview questionnaire.

Methacholine bronchoprovocation (MCh)

The requirements for initial laboratory challenge included a baseline forced expiratory volume in 1 second (FEV₁) greater than 60% of predicted value. All subjects, as determined by specific history, were free of an acute upper respiratory infection for a minimum of 6 weeks. Inhaled β_2 -agonists were

discontinued for at least 12 hours before the challenge. Administration of inhaled and systemic corticosteroids and theophylline was maintained in eight subjects. Administration of ipratropium bromide and cromolyn sodium was discontinued more than 48 hours before the MCh.

Initial and current MChs were performed by standard methods.⁹ In all challenges a DeVilbiss 646 nebulizer powered by 20 psi of compressed air (DeVilbiss Co., Somerset, Pa.) and a Rosenthal-French dosimeter (Johns Hopkins University, Baltimore, Md.) were used. The nebulization time per puff was 0.6 second. The volume of solution in the nebulizer was 1 ml for each dilution. The output of the nebulizer was 0.025 ± 0.002 ml/puff.

The best of three efforts for baseline FEV₁ and forced vital capacity (FVC) after inhalation of diluent was obtained for each subject on the Jones Pulmonaire (Oak Brook, Ill.), and the percent predicted value was calculated from the chart of Bates and Christie.¹⁰ Spirometric values were similarly obtained 3 to 5 minutes after inhalation for each dose of methacholine. Inhalation ranged from functional residual capacity to inspiratory capacity. Individuals inhaled each dose of methacholine, breathing in for 5 seconds and then exhaling to functional residual capacity. Five consecutive breaths were performed in this fashion. Subjects were seated, and nose clips were not used. Methacholine concentrations were 0.075, 0.15, 0.62, 2.5, 5.0, 10.0, and 25.0 mg/ml. The diluent contained 0.9% NaCl and 0.4% phenol.

Methacholine doses were administered at 5-minute intervals until a drop in FEV₁ of 20% or greater was obtained and sustained for 5 or more minutes compared with diluent response, or until a concentration of 25 mg/ml was achieved. PD₂₀ was defined as provocative dose, in cumulative breath units (CBU), causing in a 20% or greater decline in FEV₁. One breath unit is defined as 1 inhalation of 1 mg/ml of methacholine.⁹ Results were expressed as positive (documented PD₂₀) or negative or as the calculated PD₂₀. A positive response was considered to be a fall of 20% or more in FEV₁ at any challenge up to and including 5 inhalations of a 25 mg/ml concentration (= 225 CBU). For comparison purposes, 100 CBU PD₂₀ is a 20% or greater decrease in FEV₁ after 5 inhalations of a 10 mg/ml concentration.¹¹

Calculation of composite symptoms and treatment scores

Symptomatology was based on current respiratory symptoms obtained by interview; a system was devised to formulate symptom and treatment scores as previously used in rhinitis studies¹² and based on relative weights of severity for each parameter suggestive of asthma as shown in ■Table I. These scores were tabulated and used for further statistical analysis.

TABLE I. Calculation of composite scores

Symptom score (maximum = 24)		Treatment score (maximum = 11)	
Tightness Dyspnea Wheezing Cough	With exertion = 1* At rest = 2 At night = 3	Theophylline Inhaled bronchodilators Steroids Inhaled Systemic	PRN = 1 Daily = 2 Intermittent = 2 Maintenance = 3 Intermittent = 3 Maintenance = 4

PRN, As required.

*Numbers 1, 2, 3, or 4 indicate score assigned to an individual patient toward total score.

Data analysis

Comparisons of groups on categorical measures were done by chi square tests. For continuous variables, one-way analysis of variance and Tukey's post-hoc test were performed to identify differences among more than two groups, and paired and unpaired *t* tests were performed for comparison of two groups. Pearson's product-moment coefficient was used to analyze group means.

The SAS software package (SAS Institute, Cary, N.C.) was used for these analyses,¹³ and the Confidence Interval Analysis microcomputer program¹⁴ was used for confidence intervals.

Results

TOP

Group characteristics

Of 197 patients who returned the questionnaire, 129 indicated they would be willing to return for follow-up evaluation and repeat MCh. Seventy-eight subjects were subsequently available for this purpose. To determine whether these 78 subjects were a representative sample, their responses to the mailed questionnaire were compared with those of the 119 subjects who answered the mailed questionnaire but were not recruited for follow-up studies. The two groups were not significantly different in proportion of positive responses to any of the symptoms (data not shown). Of the 119 subjects not recruited, 59 (50%) had positive MCh results compared with 37 of 78 (47%) of the recruited group, with PD₂₀ of 51 CBU versus 60 CBU, respectively (*t* test, *p* = 0.44). For the nonrecruited group (*n* = 119) compared with the recruited group (*n* = 78), symptom scores were 7.1 versus 7.8 (*t* test, *p* = 0.53) and treatment scores were 1.7 versus 2.4 (*t* test, *p* = 0.19), respectively. We therefore concluded that the 78 subjects recruited for follow-up MCh were representative of the total group.

The recruited subjects (*n* = 78) were separated into four groups on the basis of initial and follow-up MCh results (■ Table II). In group A, MCh results were negative on both initial and follow-up challenge (N-N, *n* = 27); in group B, results were positive on initial challenge and negative on follow-up challenge (P-N, *n* = 12); in group C, results were negative on initial challenge and positive on follow-up challenge (N-P, *n* = 14); and in group D, results were positive on both challenges (P-P, *n* = 25). The groups were comparable with respect to age, sex, and minimal smoking history (see ■ Table II), and the interval of time between initial and follow-up MChs. Baseline FEV₁ was lower in the persistently positive (P-P) compared with the consistently negative (N-N) group, but FEV₁/FVC ratio

was not different, nor were mean PD₂₀s for the four sets of data generated by the responsive groups at initial and follow-up MCh challenges (■Table II).

TABLE II. Group characteristics at follow-up visit

Group* (Initial– follow-up MCh/)	Age (yr)	Sex (M/ F)	FEV ₁ (%) pred)	FEV ₁ / FVC (%)	Interval between MChs (yr)	PD ₂₀ (CBU)†	
						Initial	Follow-up
A (N-N; <i>n</i> = 27)	47 ± 3‡	12/15	97 ± 4	87 ± 1	7.1 ± 0.4	>225	>225
B (P-N; <i>n</i> = 12)	42 ± 5	3/9	87 ± 4	85 ± 1	7.0 ± 0.6	83 ± 16	>225
C (N-P; <i>n</i> = 14)	51 ± 4	4/10	83 ± 4	87 ± 1	8.6 ± 0.5	>225	76 ± 20
D (P-P; <i>n</i> = 25)	47 ± 3	6/19	79 ± 4	83 ± 2	8.0 ± 0.5	50 ± 11	43 ± 9
<i>p</i> Value§	0.54	0.39	0.003	0.18	0.17		0.13
Tukey test	NS	NS	A > D	NS	NS		NS

*Groups are designated by initial–follow-up MCh results (*N*= negative, *P*= positive). Six subjects were current smokers (A, *n*= 3; C, *n*= 1; D, *n*= 2) and 13 were ex-smokers (A, *n*= 4; B, *n*= 2; C, *n*= 3; D, *n*= 4).

†Analysis of variance is shown for the 4 groups with measureable PC₂₀s.

‡Numbers denote mean ± SEM, except for sex, which indicates numbers of male/female subjects; *p* value for sex was derived by chi square test. NS = not significant (*p* > 0.05).

§*p* Values were derived, except for sex, by one-way analysis of variance among the 4 groups, and Tukey's follow-up was used to evaluate possible differences between individual groups (*p* < 0.05).

Indications for the initial methacholine diagnostic study

Within each group, symptoms listed as present in patients referred for the initial MCh are given in ■Table III. Cough was the dominant symptom in all four groups.

TABLE III. Symptomatic indications for initial MCh

Group*	Symptom				
	Chest tightness	Dyspnea	Wheeze	Cough	
A (N-N; <i>n</i> = 27)	22†	15	4	85	

B (P-N; <i>n</i> = 12)	17	50	42	50
C (N-P; <i>n</i> = 14)	7	14	36	64
D (P-P; <i>n</i> = 25)	12	48	24	56
<i>p</i> Value‡	0.590	0.015	0.020	0.072

*Groups are defined by initial and follow-up MChs as negative (N) or positive (P).
†Numbers are percentages of subjects in each group that had the designated symptom included as an indication for ordering the test as determined by review of hospital chart.
‡Determined by chi square analysis.

Association of methacholine responsiveness with specific symptoms

The groups were evaluated on the basis of symptoms elicited from the interview questionnaire; symptoms included chest tightness, dyspnea, wheezing, and cough during exertion, at rest, or at night (■Table IV).

TABLE IV. Symptoms (percent positive) obtained by interview questionnaire*

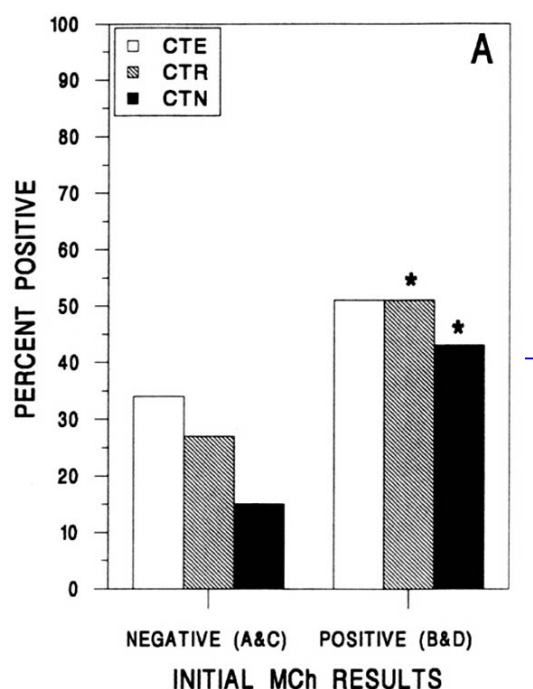
Group	Chest tightness			Dyspnea			Wheezing			Cough		
	CTE	CTR	CTN	DE	DR	DN	WE	WR	WN	CE	CR	CN
A (N-N; <i>n</i> = 27)	33	19	11	56	19	26	30	15	15	63	81	59
B (P-N; <i>n</i> = 12)	25	43	17	50	42	17	50	33	25	71	42	33
C (N-P; <i>n</i> = 14)	36	42	21	86	50	36	64	50	29	42	43	43
D (P-P; <i>n</i> = 25)	64	56	56	88	56	60	56	56	40	80	72	68
<i>p</i> Value	0.059	<u>0.047</u>	0.002	<u>0.041</u>	<u>0.037</u>	<u>0.027</u>	0.122	<u>0.014</u>	0.238	0.128	<u>0.021</u>	0.171

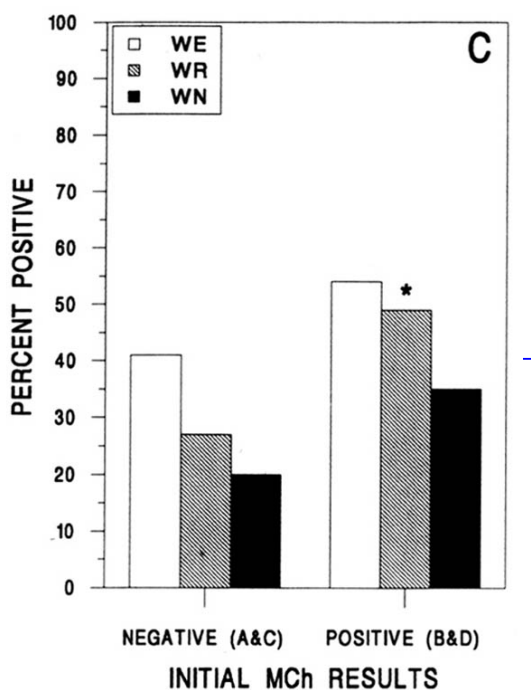
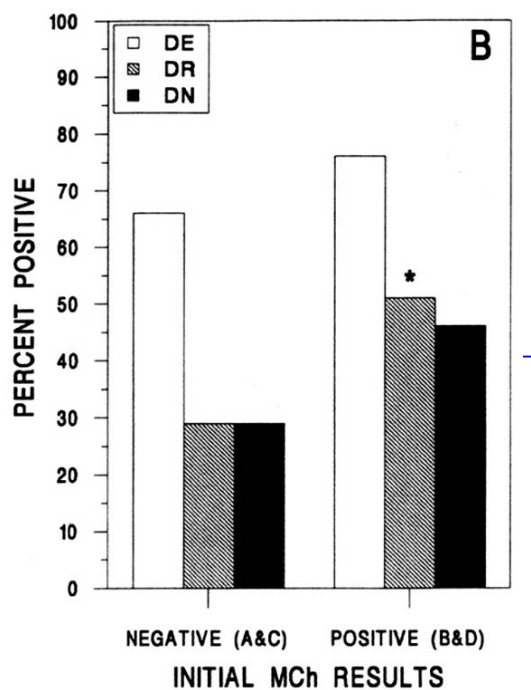
CTE, Chest tightness with exertion; CTR, chest tightness at rest; CTN, chest tightness at night; DE, dyspnea with exertion; DR, dyspnea at rest; DN, dyspnea at night; WE, wheezing with exertion; WR, wheezing at rest; WN, wheezing at night; CE, cough with exertion; CR, cough at rest; CN, cough at night.

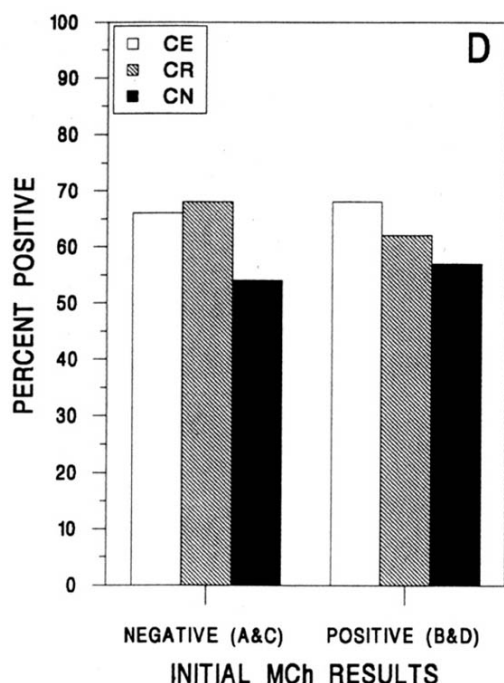
*Groups are designated by initial and current MCh results (N= negative; P= positive). Numbers are percentages of subjects within each group that had the designated symptom according to the interview questionnaire administered at the follow-up visit.
†*p* Values were derived by chi square analysis; underlined *p* values were less than 0.05.

To determine the value of MCh in predicting symptoms, either the initial or the follow-up (current) MCh results were used. MCh was used as a predictor of future symptoms by comparing initial MCh results with current symptoms (■Fig. 1). Examining the data in this manner, we found that methacholine hyperresponders during the initial challenge (*n* = 37) were significantly more likely, on follow-up 3 to 10 years later, to have chest tightness at rest (*p* = 0.026) and at night (*p* = 0.005), dyspnea at rest (*p* = 0.047), and wheezing at rest (*p* = 0.046) than were subjects with negative MCh results (*n* = 41). Cough was commonly and similarly reported by both groups.

FIG. 1. Comparisons of current symptom frequency obtained by interview questionnaire in combined groups classified as either MCh-negative (group A: N-N and group C: N-P) or MCh-positive (group B: P-N and group D: P-P) at the time of original challenge. Asterisks denote significant differences ($p < 0.05$) between subjects with positive and those with negative MCh results by chi square analysis. **A**, Chest tightness with exertion (*CTE*), chest tightness at rest (*CTR*), or chest tightness at night (*CTN*). **B**, Dyspnea with exertion (*DE*), dyspnea at rest (*DR*), or dyspnea at night (*DN*). **C**, Wheezing with exertion (*WE*), wheezing at rest (*WR*), or wheezing at night (*WN*). **D**, Cough with exertion (*CE*), cough at rest (*CR*), or cough at night (*CN*).







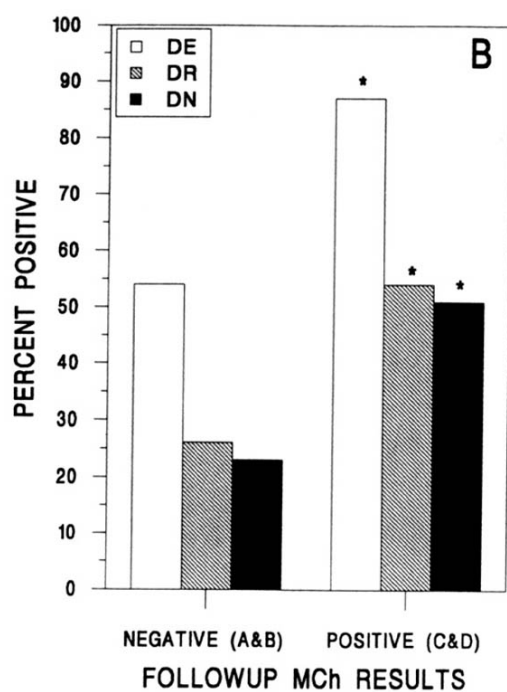
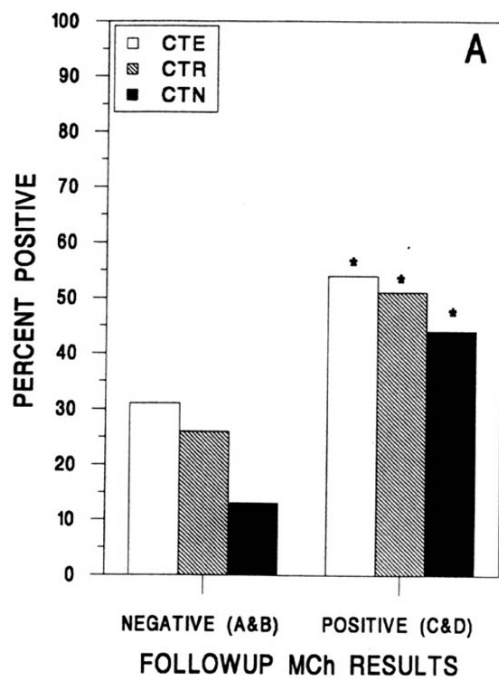
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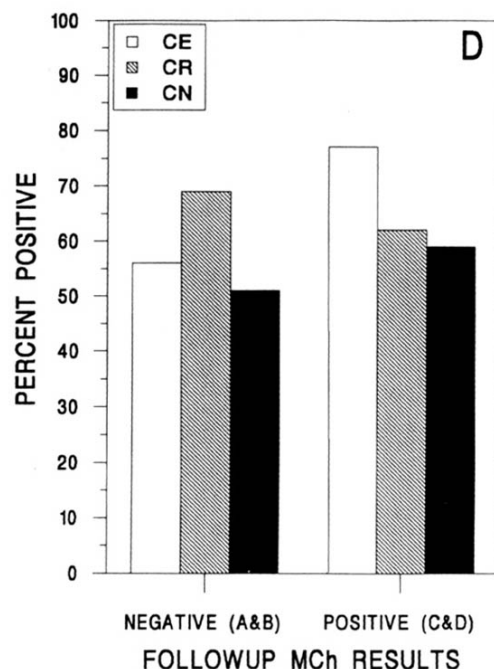
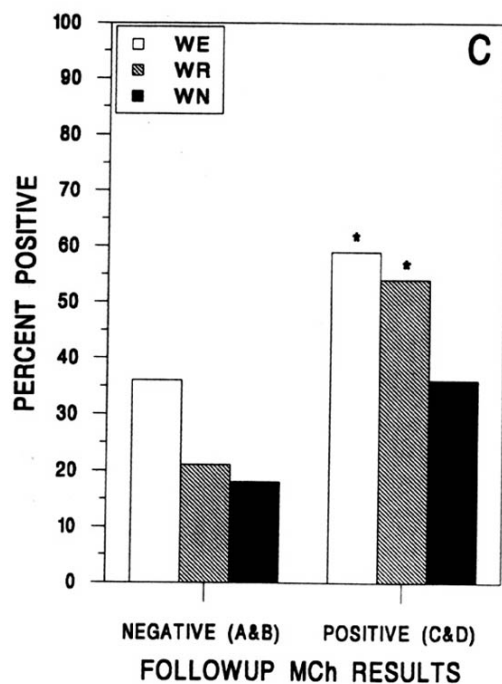
The methacholine challenge was used as a predictor of current symptoms by comparing follow-up results with symptoms elicited during the same visit (■ Fig. 2). The MCh-positive ($n = 39$) and MCh-negative ($n = 39$) groups, on follow-up challenge, were significantly different for all symptoms except wheezing at night and cough. When cough, noted on chart review as a symptom at the time of initial MCh, was compared with the presence of cough as a symptom (whether with exertion, at rest, or at night) at the time of interview questionnaire, we found that there was a similar decrease in cough prevalence for each group (group A from 85% to 78%, group B from 50% to 42%, group C from 64% to 50%, and group D from 56% to 48%). Complaints of cough or dyspnea occurring only at rest, at night, or both were not characteristic of any of the four groups (data not shown).

Methacholine responsiveness and composite symptom and treatment scores

Symptom and treatment scores for the four groups were compared with one-way analysis of variance and Tukey's post-hoc test as shown in ■ Fig. 3. The symptom and treatment scores for group D (P-P) were significantly higher than those for group A (N-N) and group B (P-N). Group C (N-P) was not significantly different from any of the other groups. Inhaled corticosteroids were used by 10 subjects (group A, 1; group B, 1; group C, 2; and group D, 6) and systemic steroids by six (group A, 1; group C, 1; and group D, 4).

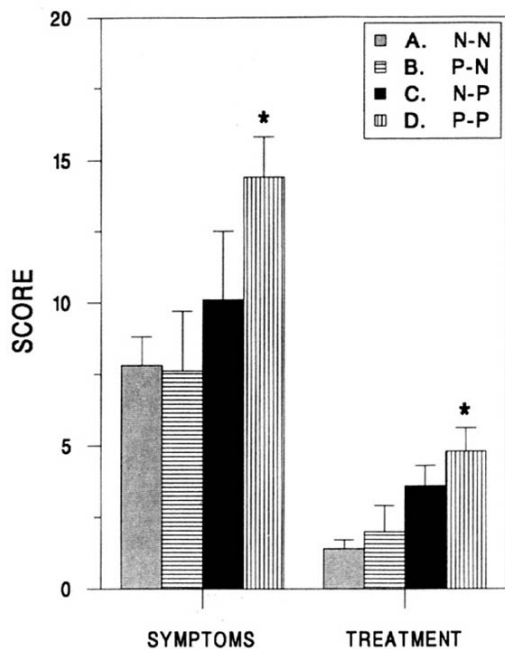
FIG. 2. Comparisons of current symptom frequency in combined groups classified as either MCh-negative (group A: N-N and group B: P-N) or MCh-positive (group C: N-P and group D: P-P) at the time of follow-up challenge. Asterisks denote significant differences ($p < 0.05$) between subjects with positive and those with negative MCh results, as determined by chi square analysis. Abbreviations as in legend to ■ Fig. 1.





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FIG. 3. Comparisons among the four subject groups of symptom and treatment scores. Bars denote standard error of the mean. Analysis of variance showed significant differences among the groups for both symptom and treatment scores ($p < 0.01$), and Tukey's post-hoc test for variable measures determined that group (P-P) was greater in scores than both group A (N-N) and group B (P-N) ($p < 0.05$); group C (N-P) was not significantly different from any other group in either symptom or treatment scores.



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When groups were combined to evaluate associations with either initial or follow-up MCh results, comparisons could be made for predictive value of the test for subsequent or concurrent symptoms, respectively (■ Table V). ■ Table V compares groups with initially negative MCh results with groups with initially positive MCh results (top) and groups with negative follow-up MCh results with those with positive follow-up MCh results (bottom). The compared groups were significantly different in all categories. MCh proved to be a reasonable predictor for higher subsequent symptom and treatment scores and an even better predictor for higher concurrent symptom and treatment scores.

TABLE V. Methacholine responsiveness and symptom and treatment scores

	Symptom score	Treatment score
Predictability for future scores		
Initial MCh neg (groups A & C; n= 41)	8.6 ± 1.1	2.1 ± 0.4
Initial MCh pos (groups B & D; n= 37)	12.2 ± 1.3	3.9 ± 0.6
t Test	p= 0.0347	p= 0.0190
CIs (95%) for difference between two groups	0.3 to 6.9	0.3 to 3.2
Association with current scores		
Follow-up MCh neg (group A & B; n= 39)	7.7 ± 0.9	1.6 ± 0.4
Follow-up MCh pos (groups C & D; n= 39)	12.9 ± 1.3	4.4 ± 0.6
t Test	p= 0.0021	p= 0.0001
CIs (99%) for difference between two groups	0.9 to 9.4	1.0 to 4.6

Values for initial and follow-up MChs are expressed as means ± SD.
neg, Negative; *pos*, positive, *CIs*, confidence intervals.

Pearson's correlation analysis

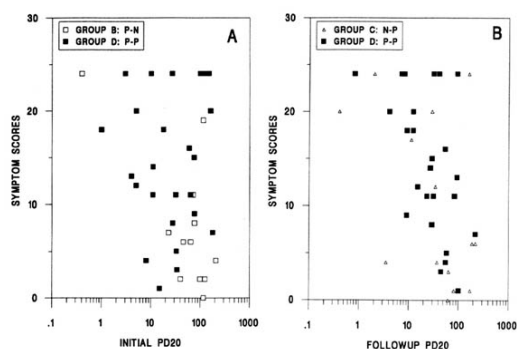
Pearson's correlation analysis was performed on paired symptom and treatment scores. When the total number of subjects was combined and analyzed, there was a fair linear relationship ($r = 0.49$, $p = 0.001$). When the four groups were analyzed separately, there was a good relationship between symptom and treatment scores for those in group C ($r = 0.65$, $p = 0.12$) and a fair relationship for group A ($r = 0.48$, $p = 0.012$); no significant linear relationship was found for either group B ($r = 0.17$, $p = 0.48$) or group D ($r = 0.35$, $p = 0.09$).

Pearson's correlation coefficient for initial and repeat PD₂₀, necessarily limited to group D (P-P), was not significant ($r = 0.25$, $p = 0.23$), indicating random variability in the degree of methacholine hyperresponsiveness with time in this group. No significant correlations could be found between methacholine hyperresponsiveness and symptom or treatment scores for any group when either initial or follow-up PD₂₀ was used, with the single exception of group D (P-P) when follow-up MCh PD₂₀FEV₁ was compared with symptom score (■ Fig. 4). We also looked for possible paired correlations between spirometric results and other continuous variables. Neither percent predicted FEV₁ nor FEV₁/FVC ratios correlated with PD₂₀s, symptoms, or treatment scores.

FIG. 4. Scatter plots showing individual PD₂₀ values for all responsive subjects and relationships between symptom scores and initial or follow-up PD₂₀. A PD₂₀ of 100 corresponds to about 10 mg/

ml methacholine. **A**, Relationships between symptom scores and initial PD₂₀ in groups B and D, both of which demonstrated positive MCh responses at the time of original challenge. Neither group showed significant correlation coefficients.

B, Relationships between symptom scores and follow-up PD₂₀ in groups C and D, both of which demonstrated positive MCh responses at the time of follow-up challenge. Group D showed a significant correlation ($r = -0.42$, $p = 0.04$), and group C did not.



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The use of nonspecific bronchoprovocation tests to assist in making the diagnosis of asthma has gained wide acceptance by clinicians. Although it is well recognized that many individuals with hyperresponsive airways have no clinical manifestations of asthma,¹⁵ negative results are generally considered to be strong evidence against this diagnosis.¹⁶ The main purpose of this study was to evaluate the subsequent course of patients with clinical indications for the test who were referred to a bronchoprovocation laboratory for assistance in making a diagnosis. One might expect that asthma would declare itself in individuals with positive MCh results and that suggestive symptoms would clear in those with negative MCh results, if the test is able to differentiate symptoms accompanying asthma from symptoms with other causes. Our working hypothesis was that patients with symptoms would differ in the progression or resolution of their symptoms with time as a consequence of the degree of airway hyperresponsiveness found at initial evaluation. Our findings did partially support this hypothesis. The MCh-positive and MCh-negative groups were statistically separable with respect to symptom and treatment scores, although almost half of each group had a continuation of cough and we found a relatively high percentage of individuals with negative MCh results who had persistent symptoms other than cough 3 to 10 years after initial MCh challenge. Chest tightness, wheezing, and dyspnea were found at rest and at night in this group, symptoms often considered strongly suggestive of clinical asthma. Thus although the groups were statistically separable, MCh was limited in its ability to predict the future course in individual patients. This was particularly true for the symptom of cough.

This study has the limitations of any retrospective study in its evaluation of the relationship of current symptoms compared with the results of MCh performed 3 to 10 years before follow-up evaluation. The questionnaire used during the follow-up interview was not used at the time of the initial study, which would have been of possible interest for paired correlations of symptoms. Our primary purpose, however, was to evaluate current symptoms in patients who were referred earlier for diagnostic MCh to assist in clinical diagnosis; these patients had symptoms suggestive of asthma but did not have documented variable airway obstruction to warrant the diagnosis. This situation is a common one in clinical practice. Referral results in selection bias because problem patients are referred. Different results would be expected in unselected normal populations or in patients with asthma or chronic obstructive pulmonary disease.

The diagnostic labels assigned to patients by the referring physician before or after initial challenge were subsequently deemed irrelevant or misleading for purposes of the study because the label was considerably influenced by the results of the MCh, and very few patients received the diagnosis of asthma on the basis of rigorous follow-up and documented reversible airway obstruction. Our purpose, moreover, was to evaluate the relationship of methacholine responsiveness to symptoms and treatment, not to confirm a diagnostic label.

The dosimeter method for methacholine challenge⁹ has been commonly used in this country, whereas investigators in Canada and the United Kingdom often use a tidal breathing method.¹⁷ The methods have been found to be comparable.¹⁸ Because of overlap in methacholine responsiveness between normal subjects and patients with asthma, various diagnostic cutoffs sacrifice either sensitivity or specificity.¹⁹ Because we were not making a case that patients with positive MCh results had asthma, it seemed advantageous to proceed to the highest dose of methacholine (25 mg/ml, 5 inhalations of which equals 225 CBU), if the subject were unresponsive below this, in order to have a

wide range of responsiveness for comparison purposes.

We have been unable to find previous reports on the primary issue, addressed here, of MCh reproducibility and significance over time in an adult population that had been referred for diagnostic MCh. The relationship of airway responsiveness to current symptoms and to clinical diagnosis, however, has been the focus of several studies. Desjardins et al.²⁰ studied 50 adult subjects who were referred to a pulmonary function laboratory for current respiratory symptoms of uncertain origin, which included wheezing (70%), chest tightness (56%), dyspnea (82%), and cough (60%), as elicited from a respiratory questionnaire. Bronchial hyperresponsiveness to histamine was present in 58% of the patients, individual current symptoms were not good predictors of airway hyperresponsiveness, and a physician's diagnosis of asthma from the respiratory questionnaire alone was not closely associated with airway hyperresponsiveness. Others have reported similar difficulties in correlating asthma diagnosis by clinicians with independent assessment of airway responsiveness. Adelroth et al.²¹ evaluated 51 consecutive new adult patients with asthma symptoms and normal spirometry results and found disagreement between a clinical assessment by the physician and the result of a methacholine test 39% of the time: 13 subjects (25%) had normal responsiveness and a clinical diagnosis of asthma, whereas seven (14%) had unexpected methacholine hyperresponsiveness. The authors concluded, nevertheless, that their findings confirmed the usefulness of the methacholine test and that a discrepant result should prompt further investigation. This conclusion appears to rest on the assumption that the objective test separated patients with asthma from those without asthma, despite clinical impressions to the contrary.

Others have reported similar findings with alternative interpretations or conclusions. The ability of respiratory physicians to diagnose the presence of airway hyperresponsiveness solely on the basis of clinical examination and spirometry results was studied in 38 patients who were first seen with symptoms that included cough, wheeze, dyspnea, chest tightness, and recurrent colds.²² Results indicated that the clinical prediction of airway responsiveness could not be relied on in decisions regarding management. A review of the usefulness of bronchial hyperreactivity measurement concluded that it is not possible, with the data at hand, to estimate the validity of hyperresponsiveness in the clinical diagnosis of asthma.²³ Relationships between pretest and posttest probability have been proposed to assist in the interpretation of bronchoprovocation tests, considered to be most crucial in patients with negative test results when the likelihood of asthma is high, based on clinical features, and in patients with positive test results who are considered unlikely to have asthma.²⁴ Resolution of the discrepancy between clinical diagnosis and methacholine responsiveness requires long-term follow-up of patients to determine to what extent the future course is predictable from MCh results, and that was the primary purpose of our study.

We found that cough with exertion, at rest, and at night was very common in all subject groups and had no correlation with methacholine responsiveness. This finding calls into question the validity of "cough-variant asthma"²⁵⁻²⁸ as a meaningful entity, if it is used simply to describe cough associated with nonspecific airway hyperresponsiveness. McFadden²⁵ reported seven patients who were first seen with cough but without dyspnea or wheezing; obstructive abnormalities, however, were found during physiologic study (percent predicted FEV₁ for the group was 53.2% ± 9.2%), which improved to normal values after a week's treatment with orally administered bronchodilators. He concluded that intermittent episodes of cough without other symptoms may represent a variant of asthma. Four years later, Corrao et al.²⁸ described six patients with chronic cough who had normal baseline spirometry

results, in contrast to McFadden's patients, but who demonstrated hyperresponsive airways with methacholine bronchoprovocation. Treatment with orally administered theophylline or terbutaline cleared the cough. The concept of cough-variant asthma as cough plus hyperresponsive airways subsequently gained wide acceptance and has been reasonably well documented as a frequent prelude to clinical asthma in children.²⁹ The mechanism of cough in asthma is unclear and may indeed be separable from, rather than dependent on, bronchoconstriction.³⁰ The question addressed here is whether the presence of hyperresponsive airways predicts the clinical course in an adult with cough. Our data indicate that it does not.

Epidemiologic studies have also evaluated relationships between symptoms or diagnoses elicited by questionnaire and airway responsiveness.^{31 32} Associations between respiratory symptom scores and the level of airway hyperresponsiveness were weak, questionnaire information was in general a poor predictor of airway responsiveness, and bronchial challenge could not reliably or precisely separate patients with asthma from the general population. According to Cockcroft and Hargreave,¹⁶ histamine or methacholine inhalation tests to exclude or confirm a diagnosis of asthma must be done at a time when a subject has had symptoms within days of the test. On the other hand, airway hyperresponsiveness has been found by others to show rather good reproducibility over months or years¹⁵ and to predate the onset of symptomatic clinical asthma by several years. Hopp et al.³³ reported 20 patients studied before and after the development of asthma, 13 of whom had moderate or strongly positive responses to methacholine before the onset of asthma an average of 3.5 years later, indicating to the authors that enhanced airway responsiveness usually precedes the development of asthma. A genetic basis for asthma was considered to be supported by their findings.

An important question is whether airway hyperresponsiveness is a significant risk factor for the development of irreversible obstructive airway disease. Brown et al.³⁴ treated 89 subjects with long-standing asthma to maximize reversibility and concluded that asthma alone can cause irreversible airflow obstruction related to the duration and severity of previous asthma; they suggested that this irreversibility may be preventable by minimizing the degree of persistent asthma. In the present study although FEV₁/FVC ratios did not differ among the groups, we found a decreased baseline FEV₁ at follow-up evaluation in the group of subjects who had positive results at both initial and follow-up MCh (group D) compared with subjects who had negative results at both MCh times (group A). We did not test the extent of reversibility. When the groups were evaluated for decreases in FEV₁ between initial and follow-up studies, we found the least decline in group B (9 ml/yr) compared with group A (38 ml/yr), group C (48 ml/yr), and group D (44 ml/yr), perhaps because of diminished nonspecific responsiveness and relative bronchodilation at the time of the follow-up study for subjects in group B who were hyperresponsive during initial MCh only.

Despite the suggestion of Gross³⁵ that we leave asthma undefined, working definitions seem necessary. An increasing tendency has been the use of nonspecific airway hyperresponsiveness as a criterion for the diagnosis of asthma, to replace documented reversible or variable airway obstruction, in patients with appropriate symptoms.²⁸ It should follow therefore that a different clinical course would be expected for subjects responsive to methacholine compared with those who are not, regardless of what diagnostic label is assigned. The results of this study lend some support for the use of MCh to help evaluate current respiratory symptoms and, to a lesser extent, to predict the future clinical course. Fewer patients who had initially negative MCh results had continuing respiratory symptoms compared with those who had initially positive MCh results, when questioned 3 to 10 years

later, with the exception of cough. Cough persisted in almost 50% of both methacholine-positive and methacholine-negative groups, suggesting that chronic cough in most adults is not associated with hyperresponsive airways. Symptoms of chest tightness, wheezing, and shortness of breath were present during follow-up in a surprising number of subjects with negative MCh results, and within the methacholine-positive (P-P) group, there was poor correlation among the degree of airway responsiveness (i.e., PD₂₀), clinical symptoms, and ongoing treatment. We conclude that interpretation of the MCh test should be cautious, especially in the evaluation of cough, in order to prevent the overdiagnosis of asthma in patients without documented reversible airway obstruction, if the term *asthma* is to retain its clinical usefulness.

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