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Relationship between bronchial airway responsiveness and clinical severity of asthma

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Summary

The minimum medication required to control symptoms was individually established in a systematic manner in 10 asthmatics. A scoring system for the severity of asthma was designed using the indices of initial airway calibre (a reflection of the degree of airway obstruction) and the minimum medication requirement; all the subjects were so scored. Bronchial airway responsiveness to histamine, methacholine and isocapnic hyperventilation of cold air was then measured in these subjects. The relationship between the level of bronchial responsiveness and the asthma severity score was examined. The mean airway responsiveness to histamine or methacholine for the subjects who required a combination of drugs was not significantly greater than that for those who required single medication intermittently or daily, while the airway responsiveness to cold air was significantly different between the subjects in the two treatment subgroups. Similarly, there was no correlation between the asthma severity score and airway responsiveness to methacholine and histamine ($r = -0.38$ and -0.48; $P > 0.1$) while a significant correlation was found with responsiveness to cold air ($r = 0.72$; $P < 0.02$). The results suggest that there is a qualitative difference between the bronchoconstriction induced in asthmatic subjects by pharmacological constrictor substances and natural physical stimuli such as cold air.

Résumé

Le minimum de traitement requis pour combattre les symptômes fut individuellement établi de manière systématique chez 10 asthmatiques. Un système d'enregistrement de la gravité de l'asthme fut mis au point à l'aide d'indices du calibre initial de la voie respiratoire (une réflexion du degré d'obstruction de la voie respiratoire) et du minimum de traitement requis; tous les sujets furent ainsi enregistres. La réaction de la voie bronchique à l'histamine, à la méthacholine et à l'hyperventilation isopanique d'air froid fut alors mesurée chez ces sujets. Le rapport entre le degré de réaction bronchique et l'enregistrement de la gravité de l'asthme fut examinée. La réaction moyenne de la voie respiratoire à l'histamine ou à la méthacholine chez les sujets qui nécessitaient un mélange de médicaments n'était pas sensiblement plus forte que chez ceux pour qui il fallait un traitement unique par intermittence ou quotidiennement tandis que la réaction de la voie respiratoire à l'air froid était sensiblement différente entre les sujets des deux sousgroupes de traitement. De même il n'y eut aucune corrélation entre l'enregistrement de la gravité de l'asthme et la réaction de la voie respiratoire à la méthacholine et à l'histamine ($r = -0.38$ et -0.48; $P > 0.1$) alors qu'il fut constaté une corrélation significative à la réaction à l'air froid ($r = 0.72$; $P < 0.02$). Les résultats suggèrent qu'il existe une différence qualitative entre la bronchoconstriction induite chez les sujets asthmatiques à l'aide de substances constrictrices pharmacologiques et de stimuli physiques naturels tels que l'air froid.

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Introduction

Non-specific bronchial airway responsiveness is increased in all asthmatic individuals with current symptoms [1]. This hyperresponsiveness is an important factor in the pathogenesis of

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bronchial asthma [2], and has been quantified by bronchial provocation tests with chemical mediators such as histamine and methacholine [1,3] and more recently by physical stimuli such as isocapnic hyperventilation of cold air [4]. Although a spectrum of bronchial responsiveness has been demonstrated among asthmatic subjects [1,4], the relationship between the degree of bronchial responsiveness and the clinical severity of asthma is not altogether clear. While some workers have demonstrated a correlation between the degree of hyperresponsiveness and parameters of clinical severity of disease such as the severity of symptoms [5], the number of previous hospital admissions [6] and treatment requirements [7,8], others have not been able to confirm such relationships [9–11]. In these studies assessments were made on patients whose asthmatic state varied from past history of attacks only, to current symptoms with poor control and frequent hospital admissions.

In this study we treated a group of mild asthmatic patients in a standard way in order to determine the minimum medication required to control symptoms, we then examined the relationship between the severity of asthma in terms of the initial airway caliber and the medication requirement, and the airway responsiveness as assessed by bronchial provocation tests with histamine, methacholine and cold air. We also tried to integrate the two parameters of severity of asthma by means of a scoring system and related this to the degree of bronchial responsiveness.

Patients and methods

The study included 10 subjects (five males, five females) who gave the characteristic clinical history of episodic dyspnoea and wheezing consistent with the American Thoracic Society definition of asthma [12]. They were all atopic, based on one or more weal-and-flare response(s) to skin-prick tests with 10 common allergens. Their ages ranged from 18 to 54 years. They all had evidence of reversibility of airway obstruction with a variation in forced expiratory volume in one second (FEV_1) greater than 15%, occuring either spontaneously or after inhalation of salbutamol aerosol. In addition, they all had an initial FEV_1 greater than 80% of the predicted normal values. The predicted values for FEV_1 for Caucasians were obtained from the nomogram by Cotes [13], while those for Nigerians were derived from the equation of Patrick and Femi-Pearse [14].

Subjects were excluded from the study on the basis of positive skin-prick test to house dust and house dust mite, which are ubiquitous allergens difficult to control, evidence of other respiratory disease, history of cigarette smoking, and symptoms severe enough to require regular oral steroid medication. They all gave informed consent and the study was approved by the Kings College Hospital, London, Ethics committee.

For each subject, the minimum medication required to control symptoms was established in the following way. No treatment was given on a regular basis if symptoms were absent or not troublesome. Such subjects were placed on inhaled salbutamol (200 μg two to four times daily) when necessary. Those with frequent symptoms or who required more than 800 μg of salbutamol in one day, and for more than two different days in a fortnight, were given regular medication with 200 μg salbutamol inhaler two to four times daily. When the highest dose of salbutamol failed to control symptoms, beclomethasone dipropionate inhaler was added in a dose of 100 μg two to four times daily. If symptoms were not controlled on salbutamol and beclomethasone inhaler, an oral xanthine was added. When satisfactory control of symptoms had been achieved on a minimum of medication for at least 2 months the subjects were deemed ready for bronchial challenge tests.

For the bronchial challenge tests the subjects each attended the laboratory at the same time on three different days within a 2-week period. The inhalation tests with histamine, methacholine and cold air were performed in a random order on the three days. For at least 6 weeks before the challenge tests, subjects had no symptoms of respiratory tract infection, influenza vaccination or exposure to any allergens to which they were sensitive. All drugs were withheld before the challenge tests for the time interval suggested by the special committee of the American Academy of Allergy [15]. Thus, bronchodilators were withheld for at least 8 h, while oral xanthines were withheld for at least 12 h prior to the tests. Sub-

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jects were only studied on the days when their baseline FEV_1 was greater than 80% of the predicted normal values, and when the variability of FEV_1 between the study days was less than 10%.

Histamine and methacholine inhalation tests were performed by the tidal breathing method similar to that described by Cockcroft *et al.* [1]. By this method, test aerosols of histamine or methacholine were generated with a Wrights nebulizer. Two millilitres of test solution were used in each case in the nebulizer container. Nebulization was achieved by driving compressed air at a flow rate of 7.5 litres per minute from a compressed air cylinder of 100 pounds per square inch pressure through the nebulizer, giving an output of 0.165–0.170 ml/min and a particle size of 1.3 μm aerodynamic mass median diameter. The aerosol was continuously delivered into a face mask held loosely over the nose and mouth, and inhaled through the mouth by quiet tidal breathing for 2 min. An aerosol of normal saline was inhaled first and the response measured by FEV_1 performed at 30 and 90 sec after the inhalation. At subsequent 5-min intervals, aerosols of histamine or methacholine, at two-fold increasing concentrations from 0.125 to 16 mg/ml, were then inhaled and spirometry repeated in the same way as in the post-saline inhalation assessment. The inhalations were discontinued when there was a fall of FEV_1 of $\geq$ 20% below the lowest post-saline value, or when the maximum concentration of histamine or methacholine had been given. Bronchial responsiveness was expressed as the provocative concentration of histamine or methacholine required to produce a 20% fall in FEV_1 (PC_{20}:FEV_1). This was read off the log concentration response curve by linear interpolation of the last two points.

Cold air generation and isocapnic hyperventilation of cold air was performed, as has been previously described from our laboratory [16]. After a baseline FEV_1 measurement, cold air challenge was given at a target minute ventilation ($\dot{V}_E$), approximately equal to 35% of the individual maximal breathing capacity (MBC). The bronchial responsiveness to cold air was expressed as the percentage fall of FEV_1 from the baseline value (ΔFEV_1%) after the cold air challenge.

In the absence of a score system suitable for assessment of this group of closely controlled mild asthmatic subjects, the 'severity' of asthma was determined by means of a scoring system based on the drug requirement for effective control of symptoms, and the baseline FEV_1 as a percentage of the predicted normal value. Subjects with a baseline FEV_1 percentage from 80 to 89% scored 50; those with a FEV_1 of 90–99% scored 25; while those with a FEV_1 $\geq$ 100% scored 10. The drug requirement was also scored such that those requiring inhaled bronchodilators occasionally scored 10; those needing inhaled bronchodilators daily scored 25; and those requiring an inhaled bronchodilator, and beclomethasone dipropionate and oral xanthine tablets daily scored 100. Higher scores indicated greater clinical severity.

The differences in mean PC_{20}:FEV_1, ΔFEV_1%, and FEV_1 as a percentage of predicted normal, between two groups were examined using Student's *t*-test, while the relationship between bronchial responsiveness and the asthma score was determined by linear regression analysis.

Results

The anthropometric, clinical and baseline physiological data for the subjects are presented in Table 1. The subjects were separated into two groups based on initial FEV_1 percentages of 80–95% and 96–110% of their predicted normal values, indicating different initial airway caliber. Table 2 shows the relationship between the initial airway calibre and the degree of bronchial responsiveness to histamine, methacholine and cold air between these groups. The difference between the mean values for the two groups for bronchial responsiveness to histamine, methacholine or cold air challenge was not statistically significant ($P > 0.1$).

The minimum drug requirement for control of symptoms in the subjects is indicated in Table 1. Those requiring beta-stimulant bronchodilators only, either intermittently or daily, were grouped together and compared with those also requiring regular inhaled steroids, with or without oral xanthines. Table 3 shows the groups and the relationship between drug requirement and the degree of bronchial responsiveness. The group requiring less medication generally had less bronchial responsiveness. The difference between the means of

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Table 1. Baseline anthropometric, clinical and physiological data of the subjects

					Baseline FEV_1			Medication			
Subjects	Age (years)	Sex	Height (m)	Weight (kg)	Predicted (litres)	Observed (litres)	% of predicted normal value	BD when necessary	BD daily	BD + BDP daily	BD + BDP + daily ASR
1	32	M	1.75	80	3.93	3.75	95.4	—	—	Yes	—
2	53	M	1.75	84	3.28	3.10	95.4	—	—	—	Yes
3	30	M	1.83	70	4.28	3.90	91.1	Yes	—	—	—
4	20	M	1.80	80.9	4.23	4.50	106.4	—	Yes	—	—
5*	48	M	1.66	83.5	2.66	2.35	88.3	—	—	—	Yes
6	21	F	1.60	52.7	3.16	3.30	104.4	—	—	Yes	—
7	28	F	1.61	64	3.0	3.15	105.0	—	—	Yes	—
8	21	F	1.63	61	3.24	3.45	106.5	Yes	—	—	—
9*	53	F	1.54	60	1.82	1.55	85.2	Yes	—	—	—
10	21	F	1.28	60	3.61	3.70	102.5	—	Yes	—	—

BD = Bronchodilator inhaler, BDP = beclomethasone dipropionate inhaler, ASR = aminophylline slow release.
*Nigerian resident in London, U.K.

Table 2. Relationship between bronchial responsiveness and initial airway calibre

	Methacholine challenge PC_{20} (mg/ml)	Histamine challenge PC_{20} (mg/ml)	Cold air challenge ΔFEV_1 %
Subjects with baseline FEV_1 between 82% and 95% of predicted normal value			
1	0.510	0.440	10.3
2	0.185	0.112	24.6
3	0.580	1.150	18.2
4	1.825	2.208	5.9
5	0.130	0.137	31.0
Mean 1	0.30	0.41	19.7
s.d. 1	0.20	0.39	7.8
Subjects with baseline FEV_1 between 96% and 110% of predicted normal value			
6	0.083	0.198	30.0
7	0.088	0.070	18.3
8	0.560	0.780	7.2
9	0.095	0.190	13.3
10	0.103	0.165	10.3
Mean 2	0.53	0.68	14.3
s.d. 2	0.67	0.80	9.1
Difference between the two groups	$t = 0.742$ $P > 0.1$	$t = 0.675$ $P > 0.5$	$t = 1.008$ $P > 0.1$

FEV_1 = First second forced expiratory volume, PC_{20} = provocation concentration producing a 20% fall in FEV_1, ΔFEV_{20}% = percentage fall from initial FEV_1 value.
t = Value for Student's t-test; P = probability value.

these groups for bronchial responsiveness to a cold air stimulus was statistically significant ($P < 0.02$). However, the difference was not statistically significant with methacholine and histamine challenge ($P > 0.05$).

Table 4 shows the relationship between the asthma score and the bronchial responsiveness to histamine, methacholine and cold air for the whole group. There was no correlation between the asthma scores and bronchial responsiveness to methacholine and histamine ($r = -0.38$ and -0.48, respectively; $P > 0.1$). The asthma scores correlate significantly with bronchial responsiveness to cold air ($r = 0.72$; $P < 0.02$).

Discussion

In this study we have assessed the clinical severity of asthma essentially by the initial airway obstruction and the minimum amount of drug required to control symptoms. The latter was established by careful systematic evaluation. The justification for this is that other parameters such as frequency and severity of acute attacks, impairment of daily activities, and frequency of hospital admissions for severe acute episodes of asthma were excluded in the selection of the subjects.

We found no significant difference in the airway responsiveness, as assessed by provocation challenge with histamine, methacholine and cold air, between the two groups of asthmatics with different initial airway calibre. Observations in a number of studies [3,17,18], that positive responses to bronchoprovocation tests are more commonly seen in patients with chronic

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Table 3. Relationship between bronchial airway responsiveness and medication requirement for control of symptoms of asthma

	Methacholine challenge PC_{20} (mg/ml)	Histamine challenge PC_{20} (mg/ml)	Cold air challenge ΔFEV_1 %
Subjects requiring bronchodilators only			
1	0.510	0.440	10.3
2	0.185	0.112	24.6
3	0.580	1.150	18.2
4	1.825	2.200	5.9
5	0.130	0.137	31.9
Mean 1	0.63	0.90	11.0
s.d. 1	0.63	0.75	4.4
Subjects requiring bronchodilators and inhaled steroids ± oral xanthine drugs			
6	0.083	0.198	30.6
7	0.088	0.070	18.3
8	0.560	0.780	7.2
9	0.095	0.190	13.3
10	0.103	0.165	10.3
Mean 2	0.20	0.19	23.1
s.d. 2	0.16	0.13	8.0
Difference between the two groups	$t = 1.479$ $P > 0.1$	$t = 2.088$ $P > 0.05$	$t = 2.965$ $P < 0.02$

FEV_1 = First second forced expiratory volume, PC_{20} = provocation concentration producing a 20% fall in FEV_1, ΔFEV_1% = percentage fall from initial FEV_1 value.
t = Value for Student's t-test; P = probability value.

obstructive bronchitis than in normal subjects, has led to criticism of the use of percentage decrease from the initial value of the index of airway calibre as an expression of the degree of bronchial reactivity. The objection was based on the probability that these responses might be merely a manifestation of the proportionately greater increase in airway resistance when a given degree of bronchoconstriction was provoked in a situation of already compromised airway calibre. Our findings, which are in agreement with those of Rubinfeld and Pain [11] who used the stimulus of methacholine in 11 asthmatics, tend to negate this criticism as one might have expected a significantly greater degree of bronchial responsiveness in subjects with greater initial airway obstruction if this was the important factor in exaggerating the responses to histamine, methacholine and cold air. Our findings are also in agreement with the everyday clinical experience when reliance on the level of airway obstruction alone often does not correlate with the severity of asthma.

The degree of bronchial responsiveness, as assessed by the stimuli of methacholine and histamine in this group of well-controlled mild asthmatics, was not related to the minimum medication requirement for the control of symptoms. While this is in agreement with the observations in a number of studies in which parameters different from ours were used in the assessment of the severity of asthma [7,9,10], it is at variance with the findings in another study in which similar bronchoconstrictor agents and parameters of assessment were employed [8]. Even though a larger number of subjects (51)

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Table 4. Relationship between bronchial responsiveness and score of severity of asthma

Subjects	Asthma score	Methacholine challenge PC_{20} (mg/ml)	Histamine challenge PC_{20} (mg/ml)	Cold air challenge $\Delta FEV_1\%$
1	75	0.510	0.440	10.3
2	125	0.185	0.112	24.6
3	35	0.580	1.150	18.2
4	35	1.825	2.200	5.9
5	150	0.130	0.137	31.9
6	60	0.083	0.198	30.9
7	60	0.088	0.070	18.3
8	20	0.560	0.780	7.2
9	60	0.095	0.190	13.3
10	35	0.103	0.165	10.3
Mean	65.3	0.42	0.54	17.1
s.d.	39.7	0.51	0.64	8.9
Correlation coefficient		$r = -0.38$	$r = -0.48$	$r = 0.72$
Probability		$P > 0.1$	$P > 0.1$	$P < 0.02$

FEV_1 = First second forced expiratory volume, PC_{20} = provocation concentration producing a 20% fall in FEV_1, $\Delta FEV_1\%$ = percentage fall from initial FEV_1 value.

was evaluated in that study, the subjects were far more heterogenous than those in our study. For example, five of their 15 subjects who required inhaled beclomethasone as well as bronchodilators had a baseline FEV_1 between 60% and 70%, and would not have satisfied the inclusion criteria in our study. If these five were excluded from that study, the distribution of bronchial responsiveness in that group would have closely matched that in the group who required bronchodilators only.

Bronchial responsiveness measurements using the stimulus of cold air in contrast to histamine and methacholine, closely reflected the clinical severity of asthma as assessed by minimum medication requirement. This finding is surprising indeed. Even though those of our subjects in the different treatment groups who responded unexpectedly to histamine also did the same following methacholine challenge, it is unlikely that the difference is simply because of the different nature of these stimuli, i.e. physical as opposed to pharmacological bronchoconstrictor stimuli. If by chance the baseline FEV_1 on the histamine and methacholine study days were consistently inconsistent, this difference could be explained. However, this is an unlikely explanation because the tests were performed only on days when the variability of FEV_1 was less than 10%. It is possible that there is a qualitative difference in the bronchoconstriction brought about by pharmacological agents and cold air. It is not unlikely that the pharmacological agents inhaled by the tidal breathing method constricted central as well as peripheral airways, while cold air inhaled at high $\dot{V}_E$ more specifically constricted a certain calibre bronchi more than the other.

In the absence of a scoring system based on non-subjective criteria suitable for our group of mild well-controlled asthmatic subjects, we further assessed the relationship between the severity of asthma and the degree of bronchial responsiveness by integrating the two parameters of the minimum drug requirement and the initial airway calibre. Even though bronchial responsiveness showed no correlation with the initial airway calibre for the three stimuli, a significant correlation was found between the asthma score and bronchial responsiveness to

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cold air, while no correlation was found following tests with methacholine and histamine similar to the assessment with the minimum drug requirement alone. The consistency of these assessments itself will appear to validate the scoring system that we have used and again support the aforementioned suspicion that a qualitative difference might in fact exist between non-specific bronchial responsiveness to cold air and pharmacological bronchoconstrictor substances. Similarly, response to the allergen challenge may be qualitatively different from the cold air challenge in that it has been shown by Tuchinda and Chai [19] that alterations in an individual's bronchial responses to allergen may be demonstrated with no significant change in the clinical severity of asthma.

It is significant that non-specific bronchial responsiveness to cold air, a natural stimulus in most temperate countries and during the harmattan seasons in some tropical countries, has been shown to be positively related to the severity of asthma. This provides corroborative evidence for the commonly observed increased drug requirement associated with increased symptoms during such climatic conditions, even though this may not be the only explanation. For example, upper respiratory tract infections are more commonly seen during the cold seasons, while indoor mould populations are higher during the rainy season [20].

Measurement of bronchial responsiveness to cold air, as opposed to histamine, methacholine or allergen, may well prove to be a reliable way of assessing the severity of asthma and thus be of some prognostic significance.

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References

1. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy 1977;7:235–43.
2. Boushey HA, Holtzman MJ, Sheller JR, Nadel JA. State of the art: bronchial hyperreactivity. Am Rev Respir Dis 1980;121:389–413.
3. Parker CD, Richard EB, Reed CF. Methacholine aerosol as test for bronchial asthma. Arch Intern Med 1965;115:452–8.
4. Deal EC, McFadden ER, Ingram RH, Breshin FJ, Jeager JJ. Airway responsiveness to cold air and hyperpnea in normal subjects and in those with hay fever and asthma. Am Rev Respir Dis 1980;121:621–8.
5. Makino S. Clinical significance of bronchial sensitivity to acetylcholine and histamine in bronchial asthma. J Allergy 1966;38:127–42.
6. Townley RG, Ryo YY, Kolotkin BM, Kang B. Bronchial sensitivity to methacholine in current and former asthmatic and allergic rhinitis patients and control subjects. J Allergy Clin Immunol 1975;56:429–42.
7. Spector SL, Farr RS. A comparison of methacholine and histamine inhalations in asthmatics. J Allergy Clin Immunol 1975; 56:308–16.
8. Juniper EF, Frith PA, & Hargreave FE. Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. Thorax 1981;36:575–9.
9. Kiviloog J. Variability of bronchial reactivity to exercise and methacholine in bronchial asthma. Scand J Respir Dis 1973;54:359–68.
10. Anderson SD, Silverman M, Konig P, Godfrey S. Exercise induced asthma. Br J Dis Chest 1975;69:1–39.
11. Rubinfeld AR, Pain MCF. Relationship between bronchial reactivity, airway caliber, and severity of asthma. Am Rev Respir Dis 1977;115:381–7.
12. American Thoracic Society. Definition and classification of chronic bronchitis, asthma, and pulmonary emphysema. Am Rev Respir Dis 1962;85:762–8.
13. Cotes JA. Lung Function. Assessment and application in Medicine, 4th edition. Oxford Blackwell Scientific Publications, 1979.
14. Patrick JM, Femi-Pearse D. Reference values for FEV_1 in Nigerian men and women: a graphical summary. Nigeria Med J 1976;6:380–5.
15. Chai H, Farr RA, Froechlich LA *et al.* Standardization of bronchial inhalation challenge procedures. J Allergy Clin Immunol 1975; 56:323–7.
16. Heaton RW, Henderson AF, Gray BJ, Costello JF. The bronchial response to cold air challenge: evidence for different mechanisms in normal and asthmatic subjects. Thorax 1983;38:506–11.
17. Klein RC, Salvaggio JE. Non-specificity of

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the bronchoconstricting effect of histamine and acetyl-beta-methylcholone in patients with obstructive airway disease. J Allergy 1966;32: 158–68.
18. Ramsdell JW, Nachtway FJ, Moser KM. Bronchial hyperreactivity in chronic obstructive bronchitis. Am Rev Respir Dis 1982;126:829–32.
19. Tuchinda M, Chai J. The effect of immunotherapy in chronic asthmatic children. J Allergy Clin Immunol 1973;51:131–8.
20. Sofowora EO. Bronchial asthma in the tropics. East Afr Med J 1970;47:434–9.

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