Differences in responsiveness to hyperventilation and methacholine in asthma and chronic bronchitis

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ABSTRACT In a previous study on 27 patients with chronic bronchitis we found that only three developed bronchoconstriction in response to hyperventilation of cold, dry air despite an increased responsiveness to methacholine inhalation. We therefore investigated bronchial responsiveness to hyperventilation with cold, dry air and methacholine in 27 patients with stable asthma who had a similar range of baseline FEV_1 values but who developed bronchoconstriction that could be reversed to give an FEV_1 more than 70% of the predicted value. Baseline FEV_1 was 0.88–3.98 l (37–114% predicted). All but one subject developed bronchoconstriction in response to hyperventilation. There was a linear relationship between baseline FEV_1 and response to methacholine ($r^2 = 0.37$, $p < 0.001$) and the relationship was significantly different from that found in the bronchitic subjects ($F_{2,50} = 24.94$, $p < 0.001$). In general, the response to methacholine was greater in the asthmatic than in the bronchitic subjects for any baseline FEV_1. The results suggest that there are different mechanisms underlying the increased responsiveness to methacholine in asthma and chronic bronchitis.

In previous studies of asthmatic patients in whom baseline spirometric values were nearly normal ($FEV_1 > 70\%$ predicted) bronchial responsiveness to methacholine correlated with the response to isocapnic hyperventilation of cold air.[1-3] The bronchial response to methacholine is also increased in patients with chronic bronchitis,[4-7] though whether this is due to the presence of asthma or secondary to the airflow obstruction is not known. When we investigated the relationship between the response to methacholine and isocapnic hyperventilation of cold air in patients with chronic bronchitis with and without airflow obstruction we found that the response to methacholine correlated with the severity of the airflow obstruction,[8] unlike the findings in asthmatic subjects with near normal baseline spirometric values. Most of these patients did not develop bronchoconstriction with hyperventilation. This discrepancy suggested that the response to

methacholine may be due to different mechanisms in asthmatic and bronchitic patients. Alternatively, the low FEV_1 may change the response to hyperventilation.

In the present study we investigated the relationship between the bronchial response to methacholine and that to isocapnic hyperventilation of cold, dry air in asthmatic patients with a range of baseline FEV_1 similar to that of the patients with chronic bronchitis studied previously.[8] We compared the relationship between the responsiveness to methacholine and the degree of airflow obstruction in the asthmatic and bronchitic groups.

Methods

SUBJECTS

Twenty seven asthmatic patients attending the Firestone Regional Chest and Allergy Unit were selected to match the range of baseline FEV_1 values (percentage of predicted values) of the patients with chronic bronchitis in a previous study[8] (table 1). The FEV_1 was greater than 70% of predicted[9] in 12 patients at the time of study and before discontinua-

Table 1 *Subject characteristics of asthmatic and chronic bronchitic patients*

		Asthma	Chronic bronchitis
Sex	Male	13	15
	Female	14	12
Age (ys)	Mean	40	56
	Range	16–62	26–79
FEV_1 (l)	Mean	2.30	2.04
	Range	0.88–3.98	0.82–3.81
FEV_1 (% predicted)	Mean	72	71
	Range	37–114	34–122
FEV_1/VC	Mean	65	61
	Range	40–93	35–84

tion of bronchodilator treatment for the study in the remainder. All subjects had a history of symptoms suggesting variable airflow obstruction; three were smokers and seven ex-smokers, and 15 were atopic. All subjects were stable at the time of the study. Baseline FEV_1 varied by up to 25% between the two study days, as some subjects were selected because they had very responsive airways. Two subjects needed no treatment, three took salbutamol as required, and the remainder needed regular bronchodilator treatment. Twelve subjects were taking inhaled beclomethasone and three prednisone. None had had a respiratory tract infection for at least four weeks or been exposed to known allergens for four weeks apart from house dust mite.

The 27 patients with chronic bronchitis are described in detail elsewhere[8] (table 1). All had a history of cigarette smoking with the development of cough and sputum in adult life, and none was thought to have asthma by the attending physician. Their baseline FEV_1 varied by less than 10% between the two study days.

STUDY DESIGN

Subjects attended the laboratory on two study days, at the same time of day, and rested for 15 minutes. They had withheld inhaled bronchodilators for six hours, short acting theophyllines for 24 hours, and long acting theophyllines for 48 hours (except for some of the more responsive subjects, who could withhold long acting theophylline only for 24 hours without intolerable falls in FEV_1). On one day a methacholine inhalation test was performed, and on the second isocapnic hyperventilation of cold air. The order of the tests depended on the availability of subject and equipment, and the two challenges were completed within two weeks.

Methods

All FEV_1 and vital capacity (VC) measurements

were made on a Collins 9 l water spirometer. The methacholine inhalation test was performed as described by Juniper *et al.*[8 10] The results, expressed as the concentration of methacholine which caused a fall in FEV_1 of 20% (PC_{20}), were obtained from the curve plotting log concentration against percentage fall in FEV_1 by linear interpolation of the last two points. One subject unable to receive methacholine because of a 60% fall in FEV_1 with saline inhalation, was assigned a PC_{20} of <0.03 mg/ml.

Isocapnic hyperventilation of subfreezing air was carried out according to the method of O'Byrne and coworkers,[18] modified from that of Strauss and coworkers.[11] The respiratory heat loss (RHL) in kilocalories/min (kcal/min) was calculated for each level of ventilation from the formula $RHL = \dot{V}E(HC\{TI-TE\} + HV\{WCI-WCE\})$, where $\dot{V}E$ = minute ventilation (l min^{-1}), HC = heat capacity of air (0.000304 kcal/min), TI and TE = inspired and expired air temperature (°C), HV = latent heat of vaporisation of water (0.00058 kcal/mg), WCI and WCE = water content of inspired and expired air (mg/l) (1 kcal = 4.184 kJ.) Inspired air was dry. Expired air was assumed to be fully saturated at the expired temperature,[12] so water content was obtained from standard saturation temperature relationships.[13] When bronchosconstriction occurred the response was expressed as the provocation dose of RHL to cause a fall in FEV_1 of 10% (PD_{10}) obtained from the log dose-response curve by linear interpolation of the last two points.

ANALYSIS

Natural logarithms of PC_{20} were used for all calculations. This transformation produces an approximately constant standard deviation over the PC_{20} range, and also helps to linearise the relationships with FEV_1 and PD_{10}. No transformation of PD_{10} was necessary. Linear regression analysis using the method of least squares was performed to compare the response to methacholine and hyperventilation of cold air in the asthmatic subjects.[14] The relationship between bronchial responsiveness (PC_{20}) and baseline spirometric values at the time of the methacholine test was compared in the asthmatic and bronchitic patients. The test of coincidence of two separate linear regression lines[15] is based on the difference in explained variation achieved by fitting two separate regression lines (with a total of four estimated parameters, two slopes, and two intercepts) to a single line through the combined data (containing only two estimated parame' ;). A large loss of fit associated with the single line is evidence of a difference in slopes or intercepts or both and is formally tested via an F statistic with two degrees of freedom in the numerator. This approach has an

advantage over separate tests for differences in slopes and intercepts, as only one test of significance is used.

Results

Hyperventilation of cold, dry air caused bronchoconstriction in all but one of the asthmatic subjects. The methacholine PC_{20} was less than 8 mg/ml in all subjects. There was a significant correlation between the PD_{10} response to hyperventilation and the methacholine PC_{20} ($r = 0.59$, $p < 0.01$) (fig 1). The one subject who did not develop bronchoconstriction with hyperventilation had only a mild increase in responsiveness to methacholine (PC_{20} 1.8 mg/ml). In contrast to the bronchitic group therefore asthmatic patients with a low FEV_1 developed bronchoconstriction in response to hyperventilation challenge.

The response to methacholine correlated with the severity of airflow obstruction in both the asthmatic and the bronchitic patients, whether this was expressed as FEV_1 (fig 2), FEV_1 % predicted, or $FEV_1/VC\%$ (table 2). When the relationship between the severity of airflow obstruction and the response to methacholine was compared in the asthmatic and bronchitic patients there was a significant difference in the relationship between the two groups (F_2, $50 = 24.94$, $p < 0.001$). The FEV_1 accounted for more of the methacholine response in the bronchitic ($r^2 = 0.74$) than in the asthmatic patients ($r^2 = 0.37$). In general, the PC_{20} was lower in the asthmatic than in the bronchitic group for any given level of airflow obstruction (fig 2).

Discussion

This study has shown that asthmatic patients with a baseline FEV_1 ranging from 37% to 114% of the predicted values develop bronchoconstriction in response to hyperventilation of cold air and that, as expected, there is a linear relationship between responsiveness to cold air and methacholine. This is in contrast to the bronchitic patients studied previously,[8] who in general did not develop bronchoconstriction with hyperventilation despite an increased responsiveness to methacholine. The two groups also differed in the relationship between baseline FEV_1 and the response to methacholine. These findings support the hypothesis that an increase in methacholine responsiveness in the presence of chronic airflow obstruction does not necessarily imply asthma, and that the mechanism of the increase in response to methacholine is different in patients with asthma and with bronchitis.
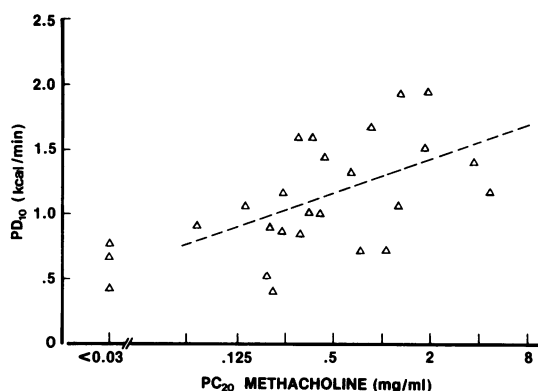

Fig 1 *Relationship between the response to methacholine (in terms of the concentration causing a fall in FEV_1 of 20%—PC_{20}) and to hyperventilation of cold dry air (in terms of the provocation dose of respiratory heat loss causing a fall in FEV_1 of 10%—PD_{10}) in the 26 asthmatic subjects. The dashed line represents the regression line. Conversion: Traditional to SI units—Heat loss: 1 kcal = 4.184 kJ.*
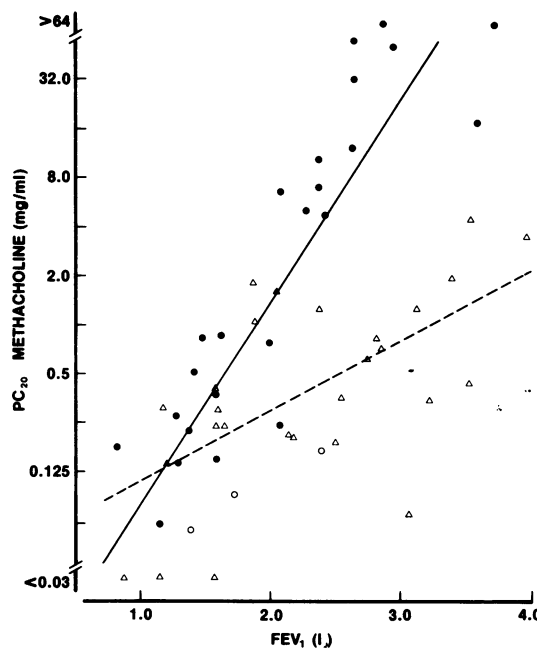

Fig 2 *Relationship between baseline FEV_1 and the response to methacholine (PC_{20}—see fig 1. △—asthmatic subjects with a bronchoconstrictor response to hyperventilation. ▲—asthmatic subjects with no bronchoconstrictor response to hyperventilation. ○—bronchitic subjects with bronchoconstrictor response to hyperventilation. ●—bronchitic subjects with no bronchoconstrictor response to hyperventilation. The regression line is represented by the dashed line for the asthmatic and the solid line for the bronchitic subjects.*

Table 2 *Linear regression analysis of airflow obstruction (independent variable) against log PC_{20} (dependent variable)*

	Asthma				Bronchitis				Difference	
	Slope	Intercept	r	p	Slope	Intercept	r	p	$F_{2,50}$	p
log PC_{20} v FEV_1	1.00	−3.22	0.61	<0.001	2.85	−5.38	0.86	<0.001	24.94	<0.001
log PC_{20} v FEV_1 % predicted	0.04	−3.71	0.62	<0.001	0.08	−5.41	0.80	<0.001	22.82	<0.001
log PC_{20} v FEV_1/VC %	0.05	−4.48	0.61	<0.001	0.12	6.74	0.74	<0.001	28.27	<0.001

PC_{20}—concentration of methacholine causing a fall in FEV_1 of 20%.

In the asthmatic subjects with a low FEV_1 the reduced maximum ventilation did not limit their ability to respond to hyperventilation of cold, dry air. Furthermore, the relationship between responsiveness to methacholine and respiratory heat and water loss was not significantly different from that of the asthmatics previously studied with mild or no airflow obstruction.[1] Thus the lack of response to hyperventilation of cold air in the bronchitic subjects is unlikely to be due to insufficient respiratory heat loss or to cooling of different areas of the respiratory tract in the presence of airflow obstruction. This suggests that the lack of bronchoconstriction in response to hyperventilation[8] in the bronchitic subjects, despite an increased response to methacholine, is a real absence of response and not an artefact produced by low sensitivity of the test procedure in the presence of airflow obstruction.

Bronchoconstriction in response to hyperventilation or exercise in asthmatic subjects implies an intrinsic abnormality in the airways. The mechanism has not been established but may depend on easier or increased release of mediators.[16-18] The demonstration of bronchoconstriction in response to hyperventilation may be a more specific test for the presence of asthma, even if there is airflow obstruction, than a pharmacological stimulus such as inhalation of methacholine. If the bronchitic subjects did not respond to hyperventilation because they did not have true asthma, then this suggests that their increased response to methacholine is due to a different mechanism from that operating in asthma. In the bronchitic group the airflow obstruction could explain about 75% of the response to methacholine ($r^2 = 0.74$), but only 35% in the asthmatic group ($r^2 = 0.37$). In the asthmatic subjects a mechanism other than airflow obstruction would appear to be the main determinant of the response to methacholine. This would not be surprising as the response to methacholine can change in asthmatics without a change in airway calibre—for example, after exposure to allergen either naturally or in the laboratory.[19 20]

Airflow obstruction may have influenced methacholine responsiveness in the asthmatics in this study in two main ways. Firstly, as suggested in

the bronchitics, there may be physical reasons—for example, on the basis of Poiseuille's law[21] or more central deposition of aerosol.[22] Secondly, if smooth muscle is already contracted less methacholine may be required to stimulate a given change in length to produce the increase in airways resistance. An estimate of the severity of smooth muscle contraction can be made from the bronchodilatation achieved after administration of a β agonist or theophylline. The asthmatic patients selected for our study had to have an FEV_1 greater than 70% predicted while having treatment. Those with the most severe airflow obstruction therefore had the greatest bronchodilator response (fig 3). As bronchodilator response correlates with responsiveness to histamine,[23 24] the relationship between FEV_1 and the response to methacholine is likely to depend on airway tone in the asthmatic group.
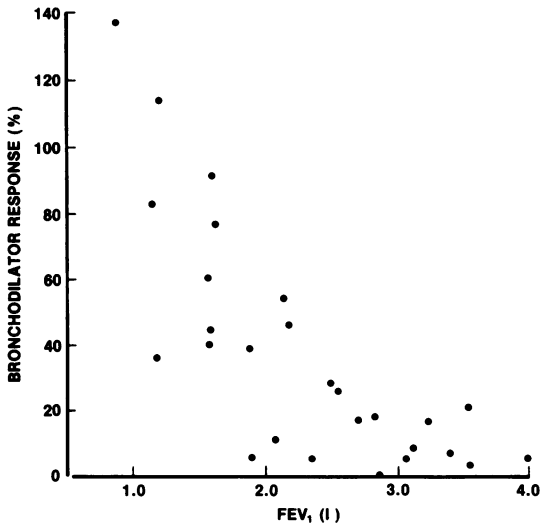
Although the demonstration of bronchoconstric-

Fig 3 *Relationship between baseline FEV_1 and bronchodilator response in the asthmatic subjects, expressed as*

$$\frac{best\ FEV_1 - baseline\ FEV_1}{baseline\ FEV_1} \times 100.$$

tion in response to hyperventilation of cold, dry air may be a more specific test than methacholine for indicating asthmatic type hyperresponsiveness in the presence of airflow obstruction, there is still the possibility that mild asthma could be missed. In this study the one asthmatic patient who did not develop bronchoconstriction in response to hyperventilation had only a mild increase in bronchial responsiveness (PC_{20} 1.8. mg/ml) despite being steroid dependent. Patients with this level of responsiveness need to achieve high levels of ventilation (greater than 60 l min^{-1}) and this would not be possible in the presence of moderately severe airflow obstruction. Further investigation of challenge tests that rely on an intrinsic abnormality in asthmatics but are easy to demonstrate in those with mild asthma is required to evaluate this hypothesis.

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