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A longitudinal study of baseline FEV_1 and bronchial responsiveness in patients with asthma

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A longitudinal study of baseline FEV_1 and bronchial responsiveness in patients with asthma. L.K. Josephs, I. Gregg, M.A. Mullee, M.J. Campbell, S.T. Holgate.

ABSTRACT: The effect of initial airway calibre on the response to bronchial provocation is unclear. Theoretically, geometric relationships within the airways might influence the measurement of responsiveness, particularly since a given change in calibre will produce a disproportionately greater reduction in flow in airways which are already narrowed.

We have examined the relationship between serial measurements of pre-challenge forced expiratory volume in one second (FEV_1) and responsiveness to methacholine (PD_{20}) in 8 children and 12 adults with asthma. Measurements were made every 2–3 wks for 12–18 months and all patients kept a daily record of symptoms and twice daily measurements of peak expiratory flow (PEF).

Spearman's rank correlation coefficient (rho) for the relationship PD_{20} *versus* pre-challenge FEV_1 was derived for each patient and varied widely within the group (range -0.22 to 0.73, mean 0.31); the strength of this correlation was not related to a patient's mean FEV_1 %predicted, but was related to the degree to which PD_{20} and pre-challenge FEV_1 themselves reflected concurrent asthma severity (mean morning PEF and mean symptom scores for the three days around each test).

This suggests that the observed relationship between pre-challenge FEV_1 and PD_{20} may be due less to the influence of airway geometric factors, which might be expected to be present in all patients, but rather that pre-challenge FEV_1 is reflecting the severity of the underlying disease. Larger studies will be needed to test this hypothesis further.

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The influence of pre-challenge airway calibre on measurements of nonspecific bronchial responsiveness is unclear. It has been difficult to study this relationship, since airway calibre can only be measured indirectly by using functional indices of airflow obstruction. Theoretically, geometric relationships within the airways might influence the measurement of responsiveness [1, 2], since resistance of an airway varies inversely with the fourth power of its radius and, thus, a given change in the calibre of already narrowed airways will produce a disproportionately greater reduction in flow. Furthermore, the presence of airflow obstruction prior to inhalation challenge with a constrictor agonist will affect the distribution of the agonist within the bronchial tree and, as a consequence, may also affect the subsequent response. The influence of these factors cannot be quantified, nor can their relative importance be determined.

Other evidence casts some doubt on the importance of baseline airway geometry as a determinant of the response to challenge. Baseline airway calibre is altered by changing posture, respiratory resistance being greater in the supine than in the sitting position [3] and this provides a physiological method for comparing responsiveness at different baseline airway diameters. In a recent report by WANG *et al.* [4], eight healthy subjects underwent bronchial challenge with histamine in both sitting and supine postures on two days; airway calibre was assessed by measuring total respiratory resistance. Baseline resistance was increased by 50% by adopting the supine posture, but this was not associated with a significant increase in histamine responsiveness.

Many studies have examined the relationship between various indices of airway calibre and bronchial responsiveness in different populations. In healthy nonsmoking subjects, some investigators have demonstrated a relationship between forced expiratory volume in one second (FEV_1) or FEV_1 as a fraction of forced vital capacity (FEV_1/FVC) and responsiveness to histamine or methacholine [5, 6], but not to cold air [7]. Others have examined the relationship in selected populations of smokers, asthmatics, or bronchitics in whom the disease itself, or factors such

as cigarette smoking, may influence or obscure the relationship between measured responsiveness and the baseline level of ventilatory function. In patients with chronic obstructive airways disease, cholinergic and histamine responsiveness have been shown to relate to baseline levels of FEV_1, FEV_1/FVC, or specific airways conductance [8–13]. In asthmatic patients the situation is much less clear, some authors reporting a modest correlation [14–17] while others have found none, especially in patients whose pulmonary function is only mildly abnormal [18–20], or in those studies which have analysed serial measurements to determine whether a within-subject relationship exists between responsiveness and changes in levels of ventilatory function [18, 21–23]. Moreover, in those studies in asthma that have established a relationship, it is unclear whether the reduction in airway calibre gives rise to hyperresponsiveness [1], or whether the latter itself determines airway calibre. It is possible that both may be separate expressions of the underlying disease, each reflecting its severity.

We have previously reported the findings of a longitudinal study investigating the relationship of responsiveness, measured at 2–3 weekly intervals, to clinical indices of asthma in 20 patients followed for a period of 12–18 months [24]. This present paper represents an extension of our original report and examines the relationship within patients between changes in pre-challenge ventilatory function and levels of responsiveness.

Methods

Patients

A description of the patients investigated and the methods used has been reported previously [24]. In summary, 12 adults and 8 children (table 1) were selected from those attending an asthma clinic held at the Aldermoor Health Centre, a general practice affiliated to the Department of Primary Medical Care of the University of Southampton. Asthma had been diagnosed in all of them on the basis of a history of episodic or persistent wheeze and shortness of breath, together with an observed variation of at least 20% in serial measurements of peak expiratory flow (PEF). All were taking anti-asthma medication at entry into the study, or had required it within the previous three months. All but one patient (no. 20) gave positive reactions to skin prick testing with one or more of 13 common allergens.

At entry into the study baseline values of forced expiratory volume in one second (FEV_1) ranged between 52–125% (mean 94%) of their predicted values using the reference values for sex, age and height reported by COTES [25]. In the two patients whose FEV_1 was <70% predicted, one (no. 7) had a history of chronic asthma which had been severe in childhood and the other (no. 5) had undergone two segmental resections in childhood for bronchiectasis, asthma having developed about 20 yrs later.

Table 1. – Patient details at entry into the study

Patient No.	Sex	Age yrs	Duration asthma yrs	Smoking Status	Smoking Duration yrs	FEV_1 % pred.
1	F	39	31	S	24	2.4 (84)
2	M	12	2	NS		2.6 (98)
3	M	66	9	Ex	30	3.8 (125)
4	F	19	15	S	3	3.0 (97)
5	M	39	8	Ex	5	2.1 (52)
6	F	34	26	NS		2.8 (93)
7	M	29	26	Ex	2	2.4 (56)
8	M	9	8	NS		2.1 (98)
9	F	8	6	NS		1.2 (86)
10	F	30	27	NS		2.9 (94)
11	M	13	4	NS		2.4 (80)
12	F	9	2	NS		1.5 (99)
13	M	11	4	NS		1.9 (96)
14	M	9	6	NS		2.0 (93)
15	M	38	8	NS		3.9 (115)
16	M	8	2	NS		1.5 (103)
17	M	27	25	Ex	<1	3.3 (77)
18	F	49	44	NS		1.8 (71)
19	F	19	15	NS		3.1 (92)
20	F	16	14	NS		2.9 (88)

S: current smoker; NS: nonsmoker; Ex: ex-smoker; FEV_1: forced expiratory volume in one second.

Measurement of ventilatory function

FEV_1 was measured with a Vitalograph dry bellows spirometer (Vitalograph Ltd, Buckingham, UK). Two or three technically correct forced expiratory manoeuvres were performed in order to obtain two repeatable FEV_1 values (difference within 100 ml), the higher of which was recorded.

Assessment of asthma severity

All patients measured their PEF every morning and evening (before taking any treatment) using a mini-Wright meter (Clement Clarke International, London, UK) and recorded the highest of three consecutive values. Diary cards were used to record these measurements of PEF, medication taken and symptoms of asthma. A daily asthma severity score was derived from the responses to eight questions concerning the degree of daytime and nocturnal wheeze, cough, or breathlessness, the amount of early morning chest tightness, the occurrence of symptoms on exposure to certain provoking factors (exercise, changes in temperature, fumes or smoke), and the extent to which symptoms restricted activities.

Methacholine bronchial provocation

Bronchial provocation was performed according to the method described by YAN *et al.* [26], with modifications as reported previously [24]. Hand-held

DeVilbiss 40 nebulizers (The DeVilbiss Co., Somerset, USA) were used to deliver a saline control and doubling doses of methacholine from 0.025 μmol to a maximum cumulative dose of 6.4 μmol. Bronchial challenge was performed provided that a subject's baseline FEV_1 was ≥60% predicted, except in the two subjects whose FEV_1 was less than this at entry into the study, in whom baseline FEV_1 was required to be ≥70% of their personal highest FEV_1. The end-point of the test was a fall in FEV_1 of >20% of the highest post-saline control level or administration of the final dose. All challenge tests were performed by a single investigator.

Duplicate measurements of provocation dose producing a 20% fall in FEV_1 (PD_{20}) were made in all patients at the start of the study, to establish the short-term repeatability of the test. The two tests were performed on consecutive days whenever possible, and at most seven days (mean 2.5 days) apart. In 17 patients data could be analysed (PD_{20} ≤12.8 μmol on both occasions), and in all but one the difference between the two PD_{20} values was within 1.24 doubling doses of methacholine; the only exception was one patient who had experienced an acute exacerbation at the time of the second measurement.

Study design

The study was performed between September 1985 and March 1987 with an interruption in December 1985/January 1986. Subjects were asked to attend whenever possible every two weeks. When clinically indicated, additional appointments were given at times of exacerbations. To avoid any circadian variation in responsiveness [27, 28], each patient attended for assessment and methacholine challenge at the same time of day on every occasion. Whenever possible, they were asked to avoid taking bronchodilator aerosols within 6 h of attendance and oral theophyllines within 12 h; other medication was continued as usual.

At every attendance, patients were questioned about the severity of their asthma since their previous assessment, and their diary cards were inspected in order to confirm the reported data. Decisions regarding treatment were based on clinical assessment and were made before bronchial challenge was performed.

Expression and analysis of data

Bronchial challenge. The results of bronchial challenge were expressed in terms of the provocation dose of methacholine which reduced the FEV_1 by 20% (PD_{20}). A dose-response curve was constructed by plotting the fall in FEV_1, expressed as a percentage of the highest post-saline value, against the cumulative dose of methacholine on a logarithmic scale. The PD_{20} was estimated by linear interpolation from the dose-response curve or, when the FEV_1 fell by <20% after the final dose of 6.4 μmol, by extrapolation for values between 6.4 and 12.8 μmol [21, 29]. Values of PD_{20} beyond this limit were recorded as >12.8 μmol. In each patient, the median PD_{20}, the absolute range and the interquartile range (encompassing 25% of values above and 25 % below the median) summarized his/her overall responsiveness during the study period.

Pre-challenge FEV_1. The highest baseline value of FEV_1 recorded prior to administration of saline was designated as the pre-challenge FEV_1. In every subject, the mean of all the estimates of pre-challenge FEV_1 was used to indicate average levels of FEV_1 during the course of the study, while its coefficient of variation summarized the degree to which pre-challenge FEV_1 varied between challenge tests.

Correction for growth (children). The observed values of pre-challenge FEV_1 in the children were corrected for increase in height during the study period [24]. This was done in an attempt to separate changes in FEV_1 due to airflow obstruction from those due to growth, since only the former might be expected to relate to any measurement of responsiveness. From measurements of height made at the start and end of the study, predicted values of FEV_1 were derived from reference values [25]. On the assumption that growth rates were linear during the course of the study, these reference values were used to estimate the expected increases in FEV_1 during this period. Observed values of FEV_1 were reduced by an amount attributable to growth based on these expected increases. Observed PEF measurements in the children were "corrected" in a comparable manner, using predicted values reported by GODFREY *et al.* [30].

Relationship between PD_{20} and pre-challenge FEV_1. Within patients, the relationship between PD_{20} and absolute values of pre-challenge FEV_1 was examined by the non-parametric Spearman's rank correlation, expressing the strength of the relationship in terms of the magnitude of Spearman's rank correlation coefficient, rho. This method of analysis was also used to assess the influence of two factors on the strength of any such correlation: 1) a patient's mean FEV_1 expressed as a percentage of predicted; and 2) the degree to which a patient's pre-challenge FEV_1 varied during the study, as reflected by its coefficient of variation.

Relationship between both PD_{20} and pre-challenge FEV_1 and asthma severity. The methods used to examine within-subject relationships between levels of methacholine responsiveness and concurrent asthma severity have been described in detail elsewhere [24]. Spearman's rank correlation was used to examine the relationship within patients between PD_{20} and the mean morning PEF for the three days around each bronchial challenge (the test day, the day before, and the day after) and to the mean asthma symptom

scores for these three days. Similar methods were used to assess the relationship within patients between pre-challenge FEV_1 and these same indices of severity. The rho value was used as a summary measure of the strength of each of these relationships in an individual and scatter plots were employed to show the association between these summary measures.

Results

The data for each of the 20 patients are shown in figure 1, listing patients in order of decreasing median PD_{20}. All were followed for between 12–18 months, except for one patient (no. 18) who was withdrawn after 9 months because of acute coronary insufficiency. Mean pre-challenge FEV_1 ranged from 55–122% predicted (mean 94%, SD 17.5) and the coefficient of variation of pre-challenge FEV_1 from 4.5–18.7% (mean 10.2%, SD 4.3).

Pt no.	Range PD_{20} methacholine µmol >12.8 6.4 1.6 0.4 0.1 0.025	No. tests	Mean pre-challenge FEV_1 %pred.	Coefficient variation pre-challenge FEV_1%
1		19	91	12.3
2		21	110	4.7
3		25	122	7.3
4		32	102	4.5
5		28	55	4.9
6		31	100	16.9
7		21	63	10.8
8		26	104	11.4
9		25	99	8.9
10		25	99	6.6
11		33	84	10.2
12		32	111	7.0
13		31	94	9.9
14		32	86	14.8
15		24	108	7.6
16		31	111	7.5
17		16	80	18.4
18		14	72	12.2
19		12	108	9.2
20		18	78	18.7

Fig. 1. – A summary of measurements of PD_{20} and pre-challenge FEV_1 (patients are listed in order of decreasing median PD_{20}). PD_{20}: the dose of methacholine required to reduce the FEV_1 by 20%: x: median PD_{20}; ⊢⊣ : range of PD_{20}; ▭ : range encompassing 25% of PD_{20} values lying above and 25% lying below the median. "No. tests": the number of completed tests available for analysis (excluding tests in which beta-agonists had been taken within 6 h). FEV_1: forced expiratory volume in one second.

Five hundred and five bronchial challenge tests were performed (mean 25 per patient, range 15–34). In nine of these, patients had taken an inhaled beta-agonist bronchodilator within the previous 6 h (one test in patient 18, two in patient 12 and three each in patients 19 and 20); these tests were excluded from analysis, since it was impossible to determine what influence the drug had had on either pre-challenge FEV_1 or PD_{20}. On eight other occasions challenge tests could not proceed, in seven cases because the pre-challenge measurements of FEV_1 were too low, and in one because of an excessive fall in FEV_1 after inhalation of the saline control.

The strength of the relationship within subjects between PD_{20} and pre-challenge FEV_1 is shown in terms of the magnitude of Spearman's rank correlation coefficient, rho, (fig. 2). Three patients (nos 1, 2 and 3) were excluded from this analysis, since their PD_{20} was indeterminable (>12.8 µmol) on >75% of occasions (fig. 1), making it impossible to examine the relationship between PD_{20} and FEV_1.

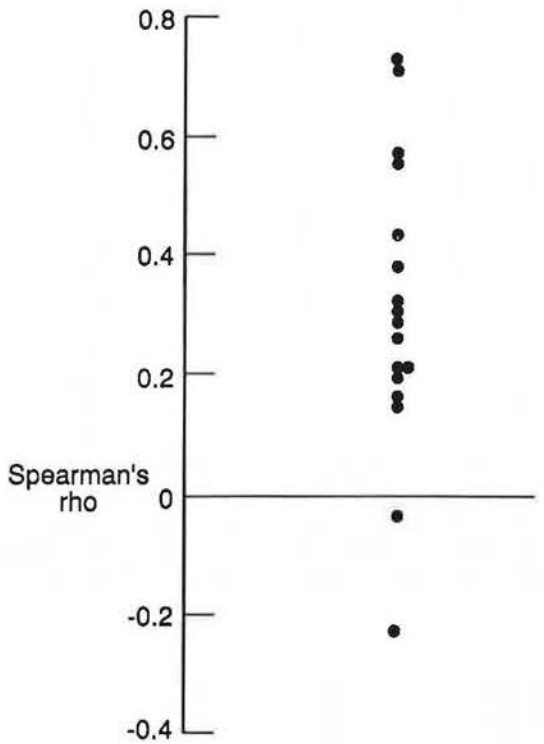

Fig. 2. – Strength of the relationship, in terms of the magnitude of Spearman's rank correlation coefficient, rho, between PD_{20} and pre-challenge FEV_1. For definitions see legend to figure 1.

In the 17 patients represented in figure 2, there was a general relationship between PD_{20} and pre-challenge FEV_1, as shown by the predominantly positive nature of the correlation, however, in only a minority of patients did the high values of Spearman's rho indicate that the relationship was strong. The strength of the correlation was not significantly related to mean levels of pre-challenge FEV_1% predicted (ρ=-0.14, p=0.61) or to the degree to which a patient's

pre-challenge FEV_1 varied during the course of the study, as assessed by its coefficient of variation (ρ=0.11, p=0.67). Patient no. 5 was excluded from the first of these analyses since his FEV_1, when compared with predicted values, was not a valid index of airflow obstruction, but rather reflected his previous lung resections.

Table 2 shows the magnitude of Spearman's rho for the relationship between PD_{20} and pre-challenge FEV_1 in the 17 patients in whom it could be calculated (data represented in fig. 2) and for the relationships between both PD_{20} and pre-challenge FEV_1 and two indices of asthma severity around the time of each bronchial challenge: mean morning PEF and mean symptom score for the three days around each test.

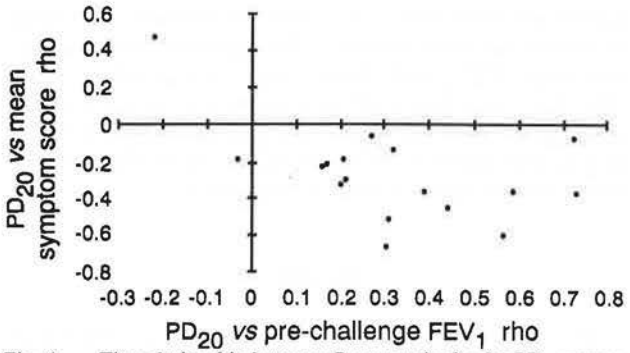

Fig. 4. – The relationship between Spearman's rho for PD_{20} *versus* pre-challenge FEV_1 and rho for PD_{20} *versus* mean symptom score for the three days around each bronchial challenge (as in fig. 3). For definitions see legend to figure 1.

Table 2. – Strength of the relationship between PD_{20} and pre-challenge FEV_1 and of the relationships between both PD_{20} and FEV_1 and two indices of concurrent asthma severity

		I	II	III	IV	V
Pt. no.	No. tests†	Spearman's rho PD_{20} *vs* pre-challenge FEV_1	Spearman's rho PD_{20} *vs* mean morning PEF#	Spearman's rho PD_{20} *vs* mean Symptom score+	Spearman's rho FEV_1 *vs* mean morning PEF#	Spearman's rho FEV_1 *vs* mean symptom score+
4	32	0.27	0.26	0.06	0.15	-0.21
5	28	0.20	0.21	-0.32	0.56*	-0.52*
6	31	0.56*	0.67*	-0.61*	0.75*	-0.63*
7	21	0.31	0.35	-0.52*	0.21	-0.35
8	26	-0.03	0.29	-0.19	0.29	-0.14
9	25	-0.22	0.10	0.47*	0.15	-0.08
10	25	0.39	0.52*	-0.37	0.43*	-0.68*
11	33	0.21	-0.11	-0.19	0.29	-0.48*
12	32	0.44*	0.31	-0.45*	0.26	-0.12
13	31	0.73*	0.66*	-0.39	0.63*	-0.43*
14	32	0.17	0.43*	-0.22	0.07	-0.43*
15	24	0.30	0.61*	-0.67*	0.60*	-0.61*
16	31	0.16	0.28	-0.23	0.29	0.07
17	16	0.21	0.26	-0.31	0.43	-0.49
18	14	0.72*	0.68*	-0.08	0.39	-0.26
19	12	0.58*	0.28	-0.37	0.39	-0.48
20	18	0.32	0.04	-0.14	0.27	-0.37

†: number of completed tests available for analysis (excluding tests in which beta-agonists had been taken within 6 h); #: mean morning PEF = mean morning PEF for the 3 days around each bronchial challenge *i.e.* the test day, the day before and the day after +: mean symptom score = mean symptom score for the 3 days around each bronchial challenge (as above); *: relationships reaching statistical significance ($p<0.05$); FEV_1: forced expiratory volume in one second; PD_{20}: provocative dose producing a 20% fall in FEV_1; PEF: peak expiratory flow.

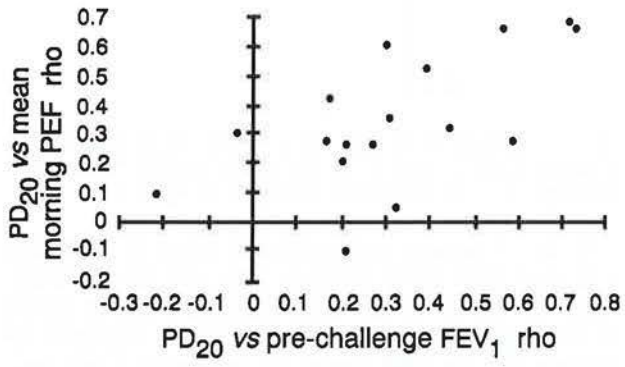

Fig. 3. – The relationship between Spearman's rho for PD_{20} *versus* pre-challenge FEV_1 and rho for PD_{20} *versus* mean morning PEF for the three days around each bronchial challenge (the day of the test, the day before and the day after). For definitions see legend to figure 1.

The strength of the correlation between PD_{20} and pre-challenge FEV_1 (table 2, column I) was related to the strength of the correlation between PD_{20} and mean morning PEF (table 2, column II), as shown in figure 3, (ρ= 0.58, p=0.015), and to the strength of the correlation between PD_{20} and mean symptom score (table 2, column III), as shown in figure 4, (ρ=-0.45, p=0.068). Similar, though more modest, associations were found for the corresponding relationships between FEV_1 and asthma severity, in that the strength of the correlation between PD_{20} and pre-challenge FEV_1 (table 2, column I) was related to the strength of the correlation between FEV_1 and mean morning PEF (table 2, column IV) (ρ=0.45, p=0.068) and to the strength of the correlation between pre-challenge FEV_1 and mean symptom score (table 2, column V) (ρ=-0.33, p=0.20). In summary, the strength of the

correlation between PD_{20} and pre-challenge FEV_1 was related to the degree to which PD_{20} and, to a lesser extent, pre-challenge FEV_1 themselves reflected concurrent asthma severity.

Discussion

When examining the findings of studies which have attempted to elucidate the relationship between bronchial responsiveness and baseline airway calibre, account must be taken of differences between them in their methods of bronchial challenge, the criteria used to assess airway calibre and responsiveness, and the populations studied.

As in the present study responsiveness is most commonly described in terms of the position of the dose-response curve, that is the provoking concentration (PC) or dose (PD) of agonist causing a certain degree of bronchoconstriction, *e.g.* a 20% fall in FEV_1. However, other indices such as the slope of the curve and the level of the plateau may give further useful information [31]. The observed relationship might also be affected by methodological differences, such as the way in which a slope is constructed from the data points, whether the stimulus is plotted on a linear or logarithmic scale, and whether the response is measured as absolute or percentage change in pulmonary function [2].

In randomly selected populations, which comprise a high proportion of normal subjects, levels of responsiveness cannot be quantified in the majority, since they lie beyond the dose-range of the provoking agent. Nevertheless, several studies have been performed in which a variety of indices have been used to assess responsiveness. RIJCKEN *et al.* [32] studied over 2,000 randomly selected subjects, of whom 25% had measurable levels of responsiveness as assessed by PC_{10} histamine. A relationship was observed between PC_{10} and baseline FEV_1 which was present after adjusting for respiratory symptoms and smoking; exclusion of subjects whose FEV_1 was <80% predicted diminished the strength of the association, though it remained significant. Other population-based studies have yielded conflicting results. Investigating healthy asymptomatic subjects, MALO *et al.* [5] found that PC_6 methacholine was related to pre-challenge FEV_1 but not to vital capacity (VC), while DEVRIES *et al.* [6] observed a relationship between PC_{10} histamine and the FEV_1/VC ratio. However, in a random sample of adults, WELTY *et al.* [7] failed to find a significant relationship between responsiveness to cold air and either FEV_1 or the FEV_1/VC ratio.

In subjects with asthma the evidence is also conflicting. A modest relationship has been shown between pre-challenge FEV_1 and PC_{20} histamine [14, 16, 17], PC_{20} methacholine [33] and the threshold dose of methacholine and histamine [15]. However, other studies have failed to confirm an association between baseline ventilatory function and levels of responsiveness. DUMAS *et al.* [19] found no correlation between pre-challenge FEV_1 or VC and PC_{20} methacholine in stable mild asthmatics with normal baseline lung function. SLY [20] found no correlation between pre-challenge PEF and exercise-induced falls in PEF in children with asthma. CADE and PAIN [22] found no relationship between pre-challenge FEV_1 and the percentage fall in FEV_1 following methacholine inhalation in a group of asthmatics, some of whom had multiple challenge tests. Similarly, RUBINFELD and PAIN [23] found no relationship between initial specific airways conductance (sGaw) and methacholine responsiveness either within the group or in those subjects in whom multiple tests were performed. Furthermore, FISH *et al.* [18] found that the variability in response to multiple bronchial challenges was unrelated to the level of pre-challenge ventilatory function (sGaw or FEV_1), though the latter showed considerable variability within-subjects.

RYAN *et al.* [34] have shown that moderate or severe hyperresponsiveness (PC_{20} <2.0 $mg \cdot ml^{-1}$ histamine) can exist when FEV_1 is "normal", *i.e.* within 10% of a subject's maximum value after an inhaled beta-agonist. Other workers have observed changes in baseline ventilatory function in the absence of changes in responsiveness [23, 24, 35], or changes in responsiveness occurring without changes in ventilatory function [24, 28, 36–39], suggesting that other factors contribute to the hyperresponsiveness.

Our own study was designed to examine longitudinally the relationship within patients between levels of responsiveness and clinical indices of asthma. We have previously reported that only a minority of patients showed a clear relationship between trends in PD_{20} methacholine and trends in asthma severity [24]. This present paper extends these findings by examining the interrelationship of these variables with pre-challenge ventilatory function. In summary, our findings suggest that, within the group, there was a general relationship between pre-challenge FEV_1 and PD_{20}, but that in only a minority of patients was the correlation strong; furthermore, we have shown that the strength of this correlation was related to the degree to which PD_{20} and pre-challenge FEV_1 themselves reflected the severity of asthma around the time of the challenge, with the strongest correlation in those patients in whom these indices were most consistently related to concurrent asthma severity. Certainly the weakness of the relationship between FEV_1 and PD_{20} in many of our patients may reflect the imperfections inherent in the measurement itself but, if airway geometric factors *per se* were important in determining responsiveness, one would expect to find a relationship the strength of which varied throughout the group, possibly being strongest in those with the most impaired lung function. Our findings would militate against this being the case, but rather might suggest that pre-challenge FEV_1 is reflecting asthma severity and the pathological processes underlying it and is only a major contributing factor in those patients in whom a clear relationship exists between severity and responsiveness: since there is no direct way of

determining underlying severity, it would be difficult to test this hypothesis further.

It has been suggested that failure to find a relationship within subjects between pre-challenge airway calibre and levels of responsiveness might be due to the occurrence of only small changes in pulmonary function in individual subjects [2]. That a more universal relationship was not revealed in the present study was unlikely to have been due to insufficient within-subject variability in pre-challenge FEV_1; moreover, the strength of the relationship was not related to the extent to which a patient's pre-challenge FEV_1 varied during the study. It is unlikely that unreliability in our methods of assessing responsiveness could account for the absence of a closer relationship between baseline FEV_1 and PD_{20}, since we have shown PD_{20} to be highly repeatable [24].

It has also been suggested that the relationship between baseline ventilatory function and responsiveness is strongest in asthmatic subjects whose FEV_1 is <70% predicted [14]. In the present study the strength of the correlation was unrelated to mean pre-challenge FEV_1 % predicted, though there were few patients whose ventilatory function was severely impaired other than at times of acute episodes.

It is important to consider the intrinsic limitations of this study before coming to generalized conclusions. Pre-challenge FEV_1 and PD_{20} are not truly independent variables, due to the methods used to derive PD_{20}, and certainly independent techniques of assessing baseline airway calibre and responsiveness would be preferable when studying their relationship. However, in this study, it is the lack of a more general relationship in our patients which has been of particular interest. Our results relate to challenge with methacholine and it is uncertain whether similar results would have been found using other bronchial provocants, particularly those which appear to rely on different underlying mechanisms for their action [40]. No single index of responsiveness can adequately summarize the dose-response relationship; our choice of PD_{20} was based on the fact that it is more repeatable than the threshold dose or concentration [41, 42], it has been very widely used and it has been shown to reflect clinical indices of asthma [16], while the slope of the curve has failed to do so [16, 23]; however, it is uncertain whether our conclusions would have been the same had other indices of responsiveness been examined.

It is possible that the mechanisms underlying hyperresponsiveness are not the same in all clinical groups. In subjects with chronic bronchitis, the relationship between baseline airway calibre and responsiveness is much stronger. RAMSDALE *et al.* [33] compared the relationship in a group of 27 subjects with asthma matched for baseline FEV_1 with a similar number of subjects with chronic bronchitis. They found a significantly stronger association in the bronchitic group, in whom initial airflow obstruction could account for about 75% of the response to methacholine, but for only 35% in the asthmatic group. They concluded that in asthmatic subjects a mechanism other than airflow obstruction appeared to be the main determinant of the response to methacholine.

The limitations of ventilatory function tests in reflecting either baseline airway calibre or levels of responsiveness make it difficult to unravel the nature of any relationship between them. While our findings suggest that a relationship exists, in many of our patients factors other than baseline airway calibre would seem to be of greater importance in determining levels of responsiveness. Further studies involving larger numbers of patients (including those with greater impairment in baseline ventilatory function) and using other bronchial provocants are needed to test this hypothesis further.

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