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Histamine dose-response curves in asthma: relevance of the distinction between PC_{20} and reactivity in characterising clinical state

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ABSTRACT The aim of the present study was to determine if the measurement of the slope of the histamine dose-response curve (bronchial reactivity) could provide useful information on the clinical state of asthma. Fifteen adult asthmatic subjects were studied twice at an interval of one year. Their clinical state was assessed by comparing their respiratory symptoms, need for medication, and FEV_1 on both visits. Histamine inhalation challenges were carried out in a similar manner both times using a standardised procedure. $PC_{20}FEV_1$ (the histamine concentration causing a 20% fall of FEV_1) and reactivity were obtained from the dose-response curves. As others have shown, we found that $PC_{20}FEV_1$ reflects clinical state. Indeed, changes of $PC_{20}FEV_1$ greater than a single two-fold dilution of histamine were shown by five of six patients who were not in a steady clinical state, and by none of the nine patients who were. Changes of $PC_{20}FEV_1$ were significantly ($p < 0.005$) more important in those who were not in a steady state in comparison with those who were. The reproducibility of reactivity was slightly better in those individuals who were in a steady clinical state as compared with those who were not. Nevertheless, changes in reactivity did not allow significant differentiation between the two groups of subjects. We conclude that $PC_{20}FEV_1$ is a more helpful index than reactivity in characterising the clinical state of asthmatics.

Bronchial reactions to inhaled non-allergic agents such as histamine and acetylcholine derivatives are characterised mainly by the dose required to produce a fixed change in a functional measurement. When FEV_1 is the functional index used, a 20% change is generally judged as significant in reflecting bronchial hyperexcitability.[1] The provocative concentration producing a 20% change in FEV_1 ($PC_{20}FEV_1$) has thus been proposed to quantify the reaction.[2]

Orehek and Gayrard[3] have suggested that inhalation dose-response curves should be studied in a pharmacological manner in which distinction is made between sensitivity (the dose at which reaction is initiated) and reactivity (the slope of the dose-response curve beyond this point). The relevance of making this distinction derives from the fact that asthmatics are distinguished from normal individuals by reactivity more than by sensitivity.[4]

It is not known whether reactivity is related to the clinical state of asthma. We therefore decided to study $PC_{20}FEV_1$ and reactivity in asthmatic subjects who either were in a steady clinical state or showed alterations in their condition.

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Methods

Fifteen adult asthmatic subjects were studied (nine men and six women) whose age ranged from 18 to 52 years (mean = 33·7; SD = 12·3, table). All subjects met the criteria for the definition of asthma proposed by the American Thoracic Society.[5] In addition, all subjects had previously shown, either spontaneously or after inhaled bronchodilator, a variation in FEV_1 of 20% or more. Skin prick tests were done with a routine battery of 15 common inhaled antigens extracts. Atopy was considered to be present whenever a patient had two or more immediate positive skin reactions. Eleven subjects were found to be atopic.

On their first visit, all these patients were in a clinical steady state and 11 of them had been included in another study.[6] At that time, they reported no exacerbation of asthma in the previous two months and no recent respiratory infection. On the

Table *Summary of data on patients studied*

Number	*Age (yr)*	*Sex*	*Atopy**	*Symptoms*		*Treatment†*		*Pred*	*FEV_1 (l)*		*ΔFEV_1‡*
				Visit 2 vs Visit 1		*Visit 1*	*Visit 2*		*Obs*	*Obs*	
				Diurnal	*Night*				*Visit 1*	*Visit 2*	
1	44	F	−	↓	−	1	0	2·2	1·35	1·45	+7
2	44	M	+	Same	−	2	1	3·5	2·70	2·70	0
3	18	F	+	↓	−	2	1	2·9	2·60	2·90	+11
4	52	M	−	Same	−	3+	3+	3·6	2·70	2·70	0
5	30	M	+	Same	−	2	1	4·0	3·70	3·65	−1
6	44	M	+	Same	−	1	1	3·9	2·90	2·85	−2
7	17	F	+	Same	−	2	3	3·2	3·75	4·00	+6
8	18	M	+	↑	−	1	1	3·8	4·50	3·60	−20
9	37	F	−	↑	+	1	2	2·4	3·10	2·90	−6
10	45	M	+	↓	−	4	4	3·9	1·65	3·05	+46
11	50	M	−	Same	−	3+	3+	3·2	3·10	3·30	+6
12	25	F	+	Same	−	1	1	2·9	2·10	2·10	+5
13	30	F	+	↓	−	3+	3+	2·9	2·50	2·65	+6
14	32	F	+	Same	−	3	3	2·5	2·40	1·80	−25
15	20	F	+	↓	−	4	3	3·1	2·20	2·50	+12

*Atopy: present if two or more immediate position skin prick reaction to a routine battery of 15 common inhaled antigens extracts.
†Treatment: 0: none; 1: beta-adrenergic stimulants or phosphodiesterase inhibitors PRN; 2: beta-adrenergic stimulants or phosphodiesterase inhibitors or sodium cromoglycate continuously; 3: aerosolised beclomethasone at 400 μg daily continuously; 3+: aerosolised beclomethasone at 800 μg daily continuously; 4: oral corticosteroids.
‡Assessed by: $\frac{FEV_1 \text{ visit 2} - FEV_1 \text{ visit 1}}{FEV_1 \text{ visit 1}} \times 100$

second visit, one year (±1 month) after the initial assessment, each of the patients was required to answer a respiratory questionnaire as regards diurnal symptoms, nocturnal waking caused by asthma, and recent respiratory infections. Special attention was paid to the two latter items, since the presence of nocturnal symptoms[7 8] has been shown to reflect an unsteady clinical state. It has also been shown that recent respiratory infections alter non-specific bronchial hyperexcitability.[9] Significant changes in the clinical state between the two visits were considered whenever at least two of the three following criteria were met: change in the respiratory questionnaire, change in drug requirement, and change of 10% or more of the initial FEV_1. Drug requirement is indeed related to the level of airway hyperexcitability.[2] Changes in FEV_1 of 10% or more exceed the percentage of reproducibility of the test and have been considered by others[10] as reflecting an unsteady clinical state.

On both visits, medications were withheld for the interval suggested by the special committee appointed by the American Academy of Allergy.[1] The two assessments were carried out at the same time of the day. Informed consent was given by each subject and the study was accepted by a medical ethics committee.

On both occasions, the subjects were asked to perform a forced expiratory manoeuvre to assess their initial FEV_1. The histamine inhalation challenge was performed in the manner suggested by Chai *et al*,[1] using the dosimeter coupled with a no 646 De Vilbiss nebuliser. The same diluent and histamine phosphate concentrations were used each time. Forced expiratory manoeuvres were carried out twice at each of 30, 90, and 180 seconds after the end of each nebulisation. In order to assess bronchial reactivity, a fall of FEV_1 to approximately 35% of the initial value was obtained, at which concentration the test was stopped. The subjects were then given two inhalations of salbutamol in aerosol and in all cases the FEV_1 was back to the initial values within 10 minutes.

The percentage fall in FEV_1 was calculated from the formula suggested by Cockcroft *et al*[2]:

$$\%\,\text{change} = 1 - \frac{\text{lowest } FEV_1 \text{ post histamine}}{\text{lowest } FEV_1 \text{ post diluent}} \times 100$$

The dose of histamine producing a 20% change in FEV_1 was calculated from the individual semi-logarithmic dose-response curve ($PC_{20}FEV_1$). In order to assess reactivity, the slope of the dose-response curve was measured as follows. The histamine concentration expressed logarithmically on the abscissa was related to the percentage change in FEV_1 on the ordinate using linear regression analysis. Only those points sustaining a progressive and steady decline in FEV_1 were included. The analysis was carried out on points inclusive between the last one plotted and backwards to the point where a change in FEV_1 greater than two standard deviations of the six post-diluent values was noticed. Three to four points were included for each curve. For each subject and at each visit, these points were within the same range of change in FEV_1, the maximal obtained fall in FEV_1 being close (±10%) at each test. Correlation coefficients of dose-response curves were calculated by the method of least squares. The

level of statistical significance required for a curve to be retained for analysis was a probability of 0·05. Those curves drawn from the FEV_1 values assessed at either 30, or 90, or 180 seconds after the end of the nebulisation, and which bore the highest statistically significant correlation coefficients, were selected to analyse reactivity. The coefficient m from the formula $y = mx + b$ was used to indicate reactivity.

Student's unpaired *t* test was used to compare the changes in $PC_{20}FEV_1$ and in reactivity between the group judged to be in a steady clinical state and that judged to be in an unsteady one.

Forced expiratory manoeuvres were carried out on a Vitalograph spirometer. Reference values for FEV_1 were taken from Goldman and Becklake.[11]

Results

The table gives the anthopometric, clinical and physiological data for each subject. Six subjects (1, 3, 8, 9, 10, and 15) were judged not to be in a clinical steady state since they fulfilled at least two of the following criteria: changes in symptoms either during the day or at night, change in drug requirement, and change in FEV_1 of 10% or more. One patient (9) reported recent respiratory infections causing night symptoms.

Figure 1 shows the individual results for $PC_{20}FEV_1$. In the nine subjects who did not experience clinical changes from one visit to the other, $PC_{20}FEV_1$ did not change by more than a single two-fold dilution of histamine, a value which is considered by others to be significant.[12 13] In this group of patients, the correlation coefficient r of the $PC_{20}FEV_1$ values for the two visits was 0·92. In contrast, five of the six subjects who were judged not to be in a clinical steady state showed significant changes in $PC_{20}FEV_1$. Changes in $PC_{20}FEV_1$ were significantly more pronounced ($p < 0·005$) in the group of subjects in an unsteady state in comparison with the group who showed no clinical changes. $PC_{20}FEV_1$ was also significantly related to the initial FEV_1 expressed in percentage of the predicted reference value ($r = 0·42$, $p < 0·02$).

Individual results for reactivity are plotted on fig 2 where distinction is made between subjects who changed their clinical state and subjects who did not.

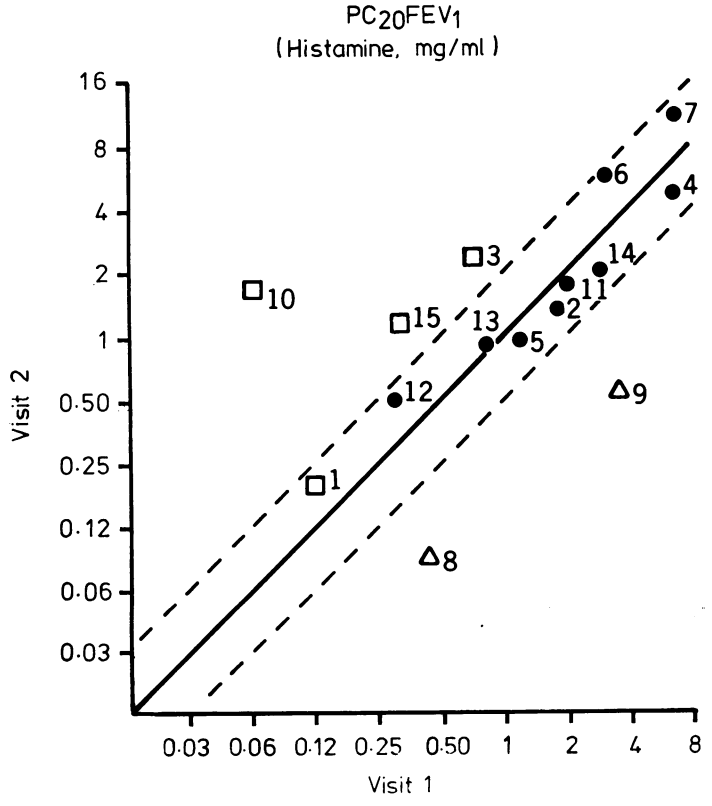

Fig 1 *Individual results on logarithmic scales of $PC_{20}FEV_1$ on each visit—*
●=patients in a clinical steady state;
□=patients whose clinical state improved on the second visit;
△=patients whose clinical state worsened on the second visit.
The non-interrupted line is the line of identity. The area between the two dashed lines represents the region of single twofold dilution difference.

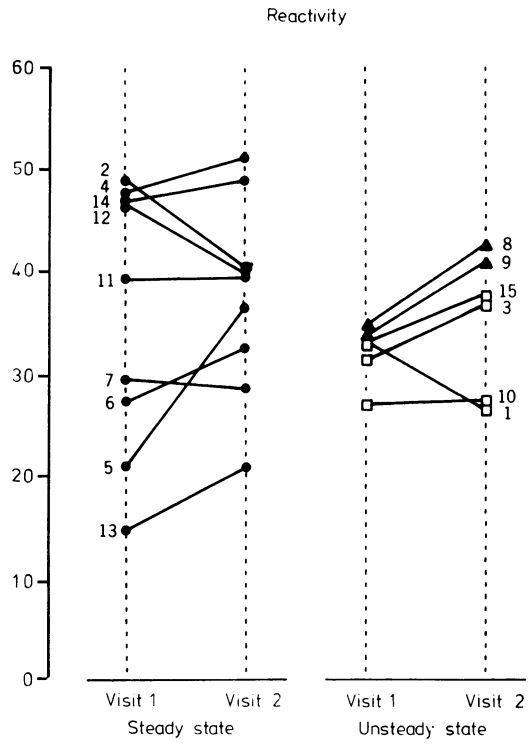

Fig 2 *Individual results of reactivity (slope m of the dose-response curve y = mx + c). There was no significant difference between changes in patients who did not change their clinical state (●) and those in patients who worsened (▲) or improved (□).*

The reproducibility of reactivity was slightly better in those individuals who were in a steady clinical state as compared with those who were not (r = 0·85 and 0·73 respectively). Nevertheless, changes in reactivity were statistically not significantly different for the two groups of subjects.

Dose-response curves of two subjects in a steady and unsteady clinical states are drawn on fig 3.

Discussion

Reviving Tiffeneau's suggestion that inhalation dose-response curves should be analysed in a true biological manner,[14] Orehek and Gayrard suggested distinguishing between the threshold dose, which they called sensitivity, and the slope of the reaction beyond this point, which they called reactivity.[3] The same workers showed that asthmatics differ from normal subjects more in terms of reactivity than of sensitivity.[4] These authors have also demonstrated that such distinction between sensitivity and reactivity can be accomplished by using FEV_1 as the physiological index reflecting the reaction.[15]

We asked ourselves if this distinction might provide clinically useful information. Our study shows that changes in $PC_{20}FEV_1$ from one visit to the other differentiate individuals who are in a clinical steady state from those who are not. Others have also found that $PC_{20}FEV_1$ or related indices reflect clinical state and the need for medication.[2 16] Changes in $PC_{20}FEV_1$, like those occurring in the pollen season[17] or after an antigen challenge,[18] have also been demonstrated in patients who were in an

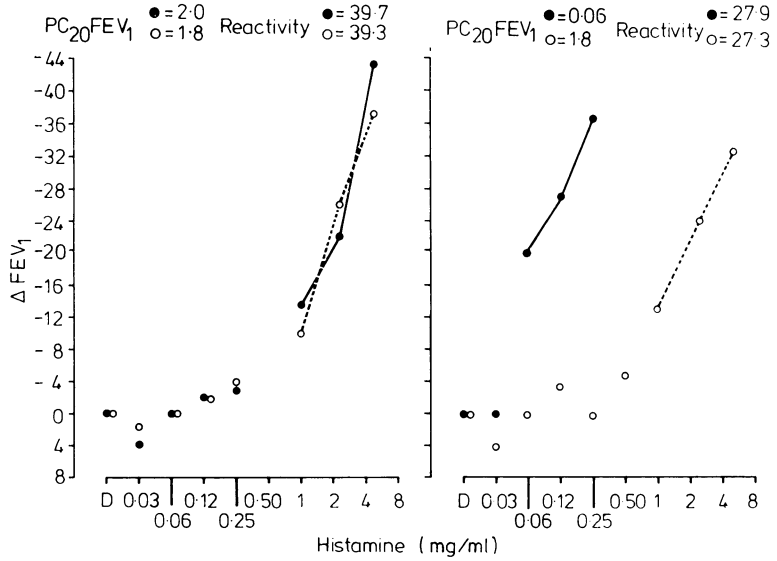

Fig 3 *Dose-response curves in two subjects. Patient 10 in a steady clinical state (left panel) showed no significant changes of $PC_{20}FEV_1$ and reactivity. Patient 11 in an unsteady clinical state (right panel) demonstrated a marked change in $PC_{20}FEV_1$ but no significant change in reactivity. (●) = first visit; (○) = second visit.*

unsteady clinical state. There was a significant relationship between $PC_{20}FEV_1$ and the initial FEV_1 ($r = 0{\cdot}42$, $p < 0{\cdot}02$) and this is also in keeping with previous findings[2 16 19 20] which relate airways hyperexcitability with the initial airways obstruction. In a previous report,[6] the correlation coefficient between $PC_{20}FEV_1$ assessed with the Dosimeter and the initial FEV_1 (expressed in percentage of the predicted value) was 0·36. This result is slightly less than the correlation coefficient of 0·42 found in the present study. This discrepancy may be explained by the fact that the two investigations did not include exactly the same subjects (only 11 of the total of 24 patients were common to the two studies).

One of the six patients who experienced changes in symptoms and need for medication demonstrated changes in FEV_1 which were less than 10% from one visit to the other. This patient (9) reported night symptoms and exhibited alterations in $PC_{20}FEV_1$. As shown by others,[7] asthmatics may well show significant airways obstruction only at night. In these individuals, the assessment of $PC_{20}FEV_1$ may better reflect the unsteady clinical state than a single measurement of FEV_1 during the day.

We show that reactivity does not appear to parallel the changes in the clinical state of our patients. Changes in reactivity were indeed not significantly different in the two groups of patients, whether they were in a steady clinical state or not. It was Orehek's opinion[4] that a valid experimental model of asthma should take account of increase in sensitivity as well as in reactivity. The conclusion of our study is that reactivity does not reflect the clinical state of asthma as defined by the clinical symptoms, drug requirement, and FEV_1.

Many features of the analysis of the non-specific inhalation dose-response curves have yet to be examined. First is the method used to calculate the slope of the dose-response curve. Orehek *et al*[4] did not use logarithmic transformation of the cumulative carbachol doses, and plotted the points on a linear scale. This procedure may tend to exaggerate the slope of the asthmatic subjects who reacted at a lower concentration and to diminish excessively the slope of the normal individuals whose threshold occurred at a higher concentration. Reanalysing their dose-response curves in a semi-logarithmic way, Orehek mentioned that reactivity nevertheless still differentiates asthmatic from normal subjects (personal communication).

The second item for discussion in the analysis of the dose-response curve is the threshold point. Orehek and his colleagues[15] suggested that the threshold should be a change of 15% in FEV_1 when this measurement is used. This threshold point appears to us rather arbitrary. We indeed showed that linear curves can be drawn by using points below the 15% limit. Fifteen per cent is well above the intrasubject reproducibility of the FEV_1. We think that for each subject, changes of FEV_1 which were beyond two standard deviations of the six post-diluent measurements should reasonably be included in the individual curve. This opinion has also been expressed by others.[21] Another point which seems important is the upper limit of changes in FEV_1 which should be included in the dose-response curve. The maximal change in FEV_1 obtained for each subject and at each visit should be similar so that curves are analysed within the same range of changes of FEV_1.

Although we observed that clinical state as defined in our study by symptomatology, drug requirement, and changes in FEV_1 does not influence reactivity, the influence of other factors such as time of day when the test is performed, previous drug administration, and inhalation of pollutants has yet to be determined.

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