Histamine induced changes in breathing pattern may precede bronchoconstriction in selected patients with bronchial asthma

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Abstract

Background **– In asthmatic patients methacholine or histamine challenge may result in more rapid and shallow breathing. Bronchoconstriction can also be associated with changes in the pattern of breathing. However, few studies, particularly in patients with asthma, have investigated the possibility that changes in the pattern of breathing may precede the onset of bronchoconstriction.**

Methods **– Eight subjects were selected from 34 consecutive asthmatic patients who had previously exhibited a significant increase in respiratory frequency (Rf) and decrease in tidal volume (VT) accompanying a 20% or greater fall in FEV_1 during a histamine bronchial provocation test. These patients also had bronchial hyperresponsiveness (histamine $PC_{20}FEV_1$ 0·1–0·25 mg/ml). VT, Rf, and the ratio of VT to Rf were evaluated breath by breath under control conditions and two minutes after inhalation of either saline or each of a series of progressively increasing concentrations of histamine. In each subject the coefficient of variation (CV) for each breathing pattern variable was calculated under control conditions and at each histamine concentration over at least 30–40 breaths. For FEV_1, VT and Rf step by step coefficients of variation were averaged and the mean (2SD) CV was considered to represent a threshold value in each patient.**

Results **– Histamine challenge resulted in increased Rf and Rf/VT, and decreased VT and FEV_1. In all but one subject change in Rf and Rf/VT beyond the threshold value preceded change in FEV_1 beyond the threshold value. The threshold concentrations of histamine for Rf and Rf/VT did not correlate with the threshold value for FEV_1.**

Conclusions **– In selected asthmatic patients a change in breathing pattern occurs prior to a change in FEV_1. These results suggest that narrowing of the airways, in terms of decrease in FEV_1, does not play a major part in the initial change in the pattern of breathing. This may be caused by direct stimulation of vagal airway receptors.**

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In sensitised dogs both specific and non-specific airway stimulation may result in more rapid and shallow breathing, which has in part been attributed to excitation of sensitised pulmonary vagal sensory receptors.[1–9] In some animal studies rapid shallow breathing was found to occur without airway obstruction,[1 4–6] and in others it preceded an increase in pulmonary resistance.[6 10–12] The reason why a change in pattern of breathing occurs before bronchoconstriction is not completely understood.

In humans asthmatic attacks may present with rapid shallow breathing,[3–17] a pattern which may be associated with ventilation-perfusion abnormalities and a moderate to marked fall in arterial Po_2 (Pao_2).[13 18] The relation of changes in breathing pattern to the onset of airways obstruction on non-specific airway stimulation remains uncertain. Some studies[19 20] show that inhaled histamine or methacholine may result in a rapid, sometimes shallow, breathing pattern[18 21–23] coincident with bronchoconstriction. In our experience this pattern occurs in about 25% of asthmatic subjects with moderate to severe bronchial hyperresponsiveness to histamine.[22 23] Very few studies have investigated whether the onset of rapid shallow breathing precedes the onset of bronchoconstriction following non-specific airway stimulation in patients with asthma.

Methods

Eight asymptomatic asthmatic patients (four men, mean (SE) age 30·2 (3) years, range 19–45) were selected from 34 consecutive patients seen at the Respiratory Section of our institute. Selection was based on the observation of a significant increase in respiratory frequency (Rf) and decrease in tidal volume (VT) accompanying a 20% decrease or more in FEV_1 during histamine challenge (fig 1). Changes in Rf and VT were considered to be significant when they exceeded the mean (SD) value by 1·65 times, calculated under control conditions. Patients in whom such a change in breathing pattern did not accompany a 20% decrease in FEV_1 did not enter the study. Smokers were excluded. At the time of the study all subjects were asymptomatic and clinically stable. Informed consent was given by each patient and the study was approved by the local ethics committee. Asthma was diagnosed on the basis of the American Thoracic Society (ATS) criteria.[24] All but two patients (nos 2 and 8) had atopic asthma with an

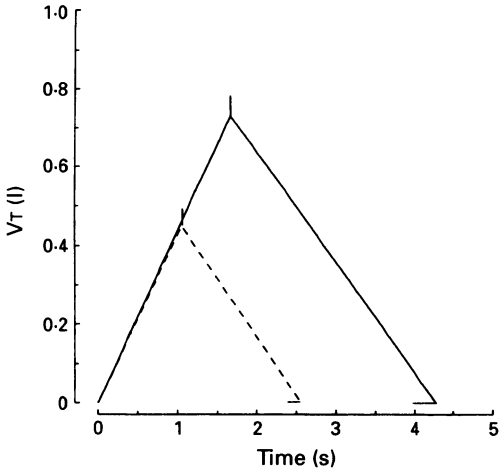

Figure 1 Schematic representation of spirogram representing the average breathing patterns of the eight patients in control conditions (solid line) and during histamine challenge (broken line). The values during histamine were recorded when FEV_1 decrease was ⩾20%. VT = tidal volume; Time = total time of the respiratory cycle. Bars represent 1SE.

immediate skin test reaction to an allergenic extract and a positive radioallergosorbent test (RAST) for the same antigen. They exhibited bronchial hyperresponsiveness ($PC_{20}FEV_1$ 0·1–0·25 mg/ml). None had a current respiratory infection; treatment with theophylline, β_2 agonists, sodium cromoglycate, and antihistamines was withheld for 24 hours before the study. Patients receiving either inhaled or oral steroids over the three months preceding the study were excluded. Subjects attended the laboratory having refrained from caffeine-containing beverages for four hours. The study was carried out during winter, and subjects had not been exposed to allergens to which they were sensitised, except house dust, for at least three weeks.

BRONCHIAL CHALLENGE

Bronchial responsiveness was tested by challenge with increasing concentrations of histamine acid phosphate in normal phosphate buffered saline, prepared by the University Hospital Pharmacy. The solutions were delivered from a nebuliser (DeVilbiss 646 nebuliser, Somerset, Pennsylvania, USA) operated at an airflow of 6 l/min. The nebulisers were calibrated and had a mean (SD) output of 0·31 (0·03) ml/min. Challenge began with saline control inhalation and continued with inhalation of doubling concentrations of histamine from 0·031 mg/ml to 0·5 mg/ml during tidal breathing over two minutes.[25] Histamine solution was stored at 4°C and nebulised at room temperature. The test was stopped at the concentration of histamine which caused a decrease in FEV_1 of at least 20% of the post saline value. From the log dose-response curve the provocative concentration of histamine required to produce a 20% fall in FEV_1 from saline ($PC_{20}FEV_1$) was determined by linear interpolation.[22 23]

MEASUREMENTS

Baseline pulmonary function testing was performed by measuring static and dynamic lung volumes with a water sealed spirometer (Pulmonet Godart). The normal values for lung volume were those of the European Community for Coal and Steel.[26]

The ventilatory pattern was evaluated breath by breath under control conditions after inhalation of saline and each concentration of histamine. The mouthpiece was connected to a heated Fleisch type 3 pneumotachograph. The flow signal was integrated into volume. From the spirogram breath by breath time and volume components of the respiratory cycle were derived: inspiratory time (TI), expiratory time (TE), total time of the respiratory cycle (TTOT), and tidal volume (VT). Respiratory frequency (Rf = 1/TTOT × 60) was also calculated. The ratio of Rf to VT quantified the extent of rapid shallow breathing.[27] This ratio has several attractive features: it is easy to measure and is independent of effort and cooperation.

Details of the technique employed have been described elsewhere.[22 23 28] The patient was seated comfortably wearing a nose clip. Subjects were relaxed with minimal visual and auditory sensory inputs. Evaluation started after a 5–10 minute period which allowed the patient to adapt to the circuit. Two minutes after either saline or each concentration of histamine was given respiratory pattern and then FEV_1 were measured. The best value of at least three reproducible (less than 4% variability) FEV_1 measurements was recorded. During the histamine challenge test patients were asked not to take deep breaths until the breathing pattern had been recorded. All periods of recording the breathing pattern excluded coughing.

Duplicate measurements of FEV_1, VT and Rf during histamine challenge were performed at the same time of day on separate days within one week.

For each subject the values presented are the means of at least 30–40 respiratory cycles recorded (1) under control conditions over the five minutes following the adaptation period; and (2) over 2–4 minutes after either saline or each concentration of histamine.

DATA ANALYSIS

One way analysis of the variance (ANOVA) was used to assess the significance of the changes in the variables employed during the histamine challenge. In addition, in each subject the coefficient of variation (CV = SD/mean × 100) was calculated for each variable over 2–4 minutes after inhalation of either saline or each histamine concentration over 30–40 breaths or more per step. Then for each variable an averaged CV and a threshold value (averaged CV (2SD)) was calculated for each subject. The same was done for FEV_1. The above procedure allowed us to compare variables with different CV. Changes in ventilatory variables and in FEV_1 with histamine were considered to be significant when they

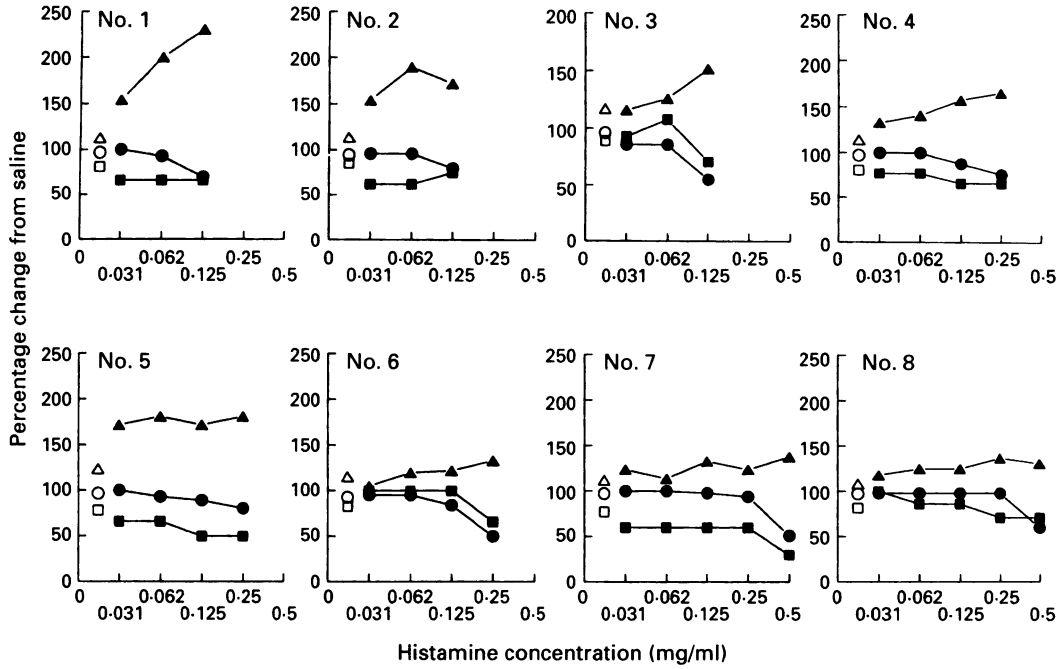

Figure 2 Individual changes in tidal volume (■), respiratory frequency (▲), and FEV_1 (●) during histamine challenge test in the eight patients. Filled symbols represent percentage change from saline; open symbols represent the values beyond which changes were considered to be significant. For explanation see text.

attained or exceeded the relevant threshold value. The histamine concentration (Hc) at which FEV_1, Rf, and Rf/VT reached the threshold value ($HcFEV_{1th}$, $HcRf_{th}$, $Hc(Rf/VT)_{th}$, respectively) was assessed by regression analysis (the least square method). The significance of the differences between the logarithmic transformation of $HcFEV_{1th}$, $HcRf_{th}$, and $Hc(Rf/VT)_{th}$ was assessed by ANOVA and Tukey *t* test.

The reproducibility of duplicate measurements of Rf, VT, and FEV_1 was assessed by two way analysis of variance.

Results

The patients had normal lung function under control conditions: mean FEV_1 was 92·7 (6·1)% predicted, vital capacity (VC) was 95·7 (4·3)% predicted, and FEV_1/VC was 79·9 (3·3)%. Mean $PC_{20}FEV_1$ was 0·21 (0·02).

Figure 2 shows individual changes in VT, Rf, and FEV_1 during the histamine challenge test; values are expressed as percentage of saline. In each patient breathing pattern variables either decreased (VT) or increased (Rf and Rf/VT) significantly ($p<0·001$, ANOVA for each variable), while FEV_1 significantly decreased ($p<0·0001$, ANOVA).

Table 1 Analysis of variance for coefficients of variation of VT, Rf, Rf/VT ratio and FEV_1

		Mean square	*F ratio*	*p*
VT	Between subjects	43·55	3·14	<0·01
	Within subjects	13·85		
Rf	Between subjects	41·9	4·911	<0·001
	Within subjects	8·55		
Rf/VT	Between subjects	137·19	5·092	<0·001
	Within subjects	26·94		
FEV_1	Between subjects	3·65	2·676	<0·05
	Within subjects	1·36		

VT = tidal volume; Rf = respiratory frequency; FEV_1 = forced expiratory volume in one second.

In order to assess the variability during the test of FEV_1 and breathing pattern components, the coefficient of variation for each variable was calculated for each histamine concentration and then averaged in each patient. The between subjects and within subjects analysis of the variance for the coefficients of variation of VT, Rf, Rf/VT, and FEV_1 is shown in table 1. It is evident that the coefficient of variation for FEV_1 had the lowest value for both between and within subjects variability.

In each subject the mean (2SD) coefficient of variation for each subject was considered as a threshold value and changes in ventilatory variables and FEV_1 were considered to be significant when they achieved or exceeded the threshold value: for instance, in patient no. 2 (fig 2) at histamine concentration of 0·031 mg/ml Rf was 154% of saline; the averaged coefficient of variation was 8·2% (2·7 SD), the threshold value being 13·6% (that is, $8·2+(2·7\times 2)$). Therefore, the Δ% increase from saline (54) was 3·4 times the threshold value (13·6). From fig 2 it is evident that, in all cases but one, change in Rf beyond the threshold value preceded change in FEV_1 beyond the threshold value, and in the remaining case (no. 3) the opposite was found. A similar pattern was found for Rf/VT. In some circumstances VT, Rf/VT ratio, or both, worsened as soon as FEV_1 decreased markedly. This pattern was evident in patient nos 3, 6, and 7.

More importantly, we calculated the histamine concentration at which FEV_1, Rf, and Rf/VT attained their threshold values: these concentrations are referred to as $HcFEV_{1th}$, $HcRf_{th}$, and $Hc(Rf/VT)_{th}$ respectively. Values are reported in table 2 where it is evident that $HcRf_{th}$ and $Hc(Rf/VT)_{th}$ were significantly lower than $HcFEV_{1th}$ (one way analysis of variance and Tukey *t* test). In other words, Rf and Rf/VT required lower histamine concen-

Table 2 Concentrations of histamine (mg/ml) at which changes in FEV_1, Rf, and Rf/VT ratio reached the threshold value

Patient	$HcFEV_{1th}$	$HcRf_{th}$	$Hc(Rf/VT)_{th}$
1	0·046	0·0077	0·0029
2	0·069	0·0085	0·0041
3	0·0097	0·04	0·012
4	0·076	0·014	0·010
5	0·047	0·011	0·0073
6	0·08	0·053	0·062
7	0·15	0·015	0·0077
8	0·247	0·014	0·022
Mean	0·09	0·02	0·016
SD	0·07	0·01	0·01

$HcFEV_{1th}$, $HcRf_{th}$, and $Hc(Rf/VT)_{th}$ = histamine concentrations at which changes in FEV_1, Rf, and Rf/VT, respectively, attained the threshold value.

trations than FEV_1 to vary significantly. It is of interest that Rf and Rf/VT did not differ significantly in their sensitivity. $HcFEV_{1th}$ did not relate to either $HcRf_{th}$ or $Hc(Rf/VT)_{th}$.

Table 3 shows the reproducibility of duplicate measurements of $HcFEV_{1th}$, $HcRf_{th}$ and $Hc(Rf/VT)_{th}$: two way analysis of variance showed that the within subject variability was not significant and was always lower than the between subject variability.

Discussion

A number of variables could interfere with the pattern of breathing, either before or during a histamine challenge test. In the present study the following argues against the variability being due to other factors. Firstly, considering anxiety which causes rapid and shallow breathing, and learned behaviour and experience which act in preventing it, efforts were made to limit any stress and to relax the subject with a minimum of visual and auditory stimulation. Secondly, administration of saline did not affect ventilation; and, thirdly, when histamine challenge tests were repeated within one week the respiratory pattern did not change.

The use of a mouthpiece and noseclip may be criticised. A mouthpiece has been reported to alter the breathing pattern[29] by increasing tidal volume (VT) and shortening respiratory frequency (Rf). However, a lack of mouthpiece effect during bronchoconstriction has also been reported in patients with asthma.[16] One could argue, therefore, that the decrease in VT and increase in Rf from the control conditions to histamine was the result of the loss of mouthpiece effect coincident with bronchoconstriction. Because the increase in Rf was noted both before and after the decrease in FEV_1, however, we suspect that a mouthpiece effect was not primarily involved in the observed increase in Rf.

Table 3 Reproducibility of duplicate measurements: two way analysis of variance

		Mean square	F ratio	p
$HcFEV_{1th}$	Between subjects	0·124	53·73	0·001
	Within subjects	0·00008	0·347	NS
	Residual	0·00023		
$HcRf_{th}$	Between subjects	0·0004	9·1	0·005
	Within subjects	0·0000008	0·017	NS
	Residual	0·000047		
$Hc(Rf/VT)_{th}$	Between subjects	0·0006	11·34	0·005
	Within subjects	0·000001	0·26	NS
	Residual	0·000053		

Abbreviations as in table 2.

Although FEV_1 is not the most sensitive functional index of airway calibre, it has a high level of reproducibility which makes it reliable for clinical use.[30] Airway resistance, which also assesses airway calibre,[11 16 18 21 31] might be preferable because of its greater sensitivity. However, the reproducibility during histamine challenge is less satisfactory than FEV_1.[31] We are certainly aware that FEV_1 is not capable of ruling out a lesser degree of airway constriction too small to cause reduction in FEV_1. We cannot therefore rule out some association between bronchoconstriction and initial change in breathing pattern. Nevertheless, the same criticism could be made whatever the method used in assessing bronchoconstriction.

Previous studies in animals indicate that histamine increases the resistance of the lung and causes rapid shallow breathing.[1 6-8] Some of these studies, however, showed that pretreatment with a bronchodilator prevented an increase in lung resistance without any effect on the increase in Rf and decrease in VT with histamine or antigen inhalation.[1 7] Cotton *et al*[4] showed that the tachypnoeic hyperpnoeic response to antigen challenge is a vagally mediated reflex and is separable from bronchoconstriction. In fact, vagally blocked dogs challenged with the antigen exhibited an increase in airway resistance with no change in Rf or VT.[4] These[1 6-8] and other observations[3] seem to indicate that, by stimulating the vagal receptors directly, histamine may modify the breathing pattern. Consistent with this hypothesis, Paré *et al*,[10] Michoud *et al*,[6] and Hogg *et al*[11] have shown that in a canine model increase in Rf precedes any measurable change in airway resistance by about 60 seconds, the increase in lung resistance being coincident with the plateau of the Rf response. These and more recent data[12] support the contention that: (1) increase in Rf and bronchoconstriction are mediated independently, and (2) the initial stimulus for increased Rf is not the mechanical distortion of the airway produced by bronchoconstriction. The release of histamine, and perhaps other mediators, is likely to play a major part.[4-6 10 11]

Experiments in humans are difficult to interpret. McFadden[32] showed that an increase in ventilation, cough, and dyspnoea may occur without clinically apparent wheezing in patients with reversible airway obstruction. Guz[33] in a patient with asthma noted that the inhalation of histamine before and after vagal block produced equivalent amounts of bronchoconstriction, but histamine induced hyperventilation and dyspnoea were abolished. These findings suggest that abnormalities in breathing pattern in asthma are related to lung receptor stimulation and are not due to changes in lung mechanics.

In previous papers in humans[18 19 21-23] the measurement of breathing pattern coincided with the dose of agonist which produced a substantial airway narrowing. By applying breath by breath and step by step analysis of breathing pattern we have shown that change

in breathing pattern, increase in Rf and Rf/VT ratio, may precede even a small decrease in FEV_1. These data are somewhat in contrast with those of Chadha *et al*[20] who showed that, after exposure to ultrasonically nebulised distilled water, an increase in respiratory resistance, which coincided with an increase in VE, was not accompanied by a significant increase in Rf. The two studies are difficult to compare, however, because different stimuli for provoking bronchoconstriction were employed.

In the circumstances of the present study we speculate that Rf and Rf/VT variables are sensitive in detecting abnormalities in bronchial mucosa. In fact, the histamine concentrations at which Rf and Rf/VT attained the threshold value ($HcRf_{th}$ and $Hc(Rf/VT)_{th}$, respectively) significantly differed from, and were not related to, $HcFEV_{1th}$. Thus, it would appear that the mechanism(s) responsible for the initial change in Rf is independent of airway narrowing. A direct stimulation of airway vagal receptors could be involved.[13]

Although the effects of inhaled histamine are not the same as those which take place in a spontaneous episode of bronchospasm, we feel that the present data may have some clinical implications. Firstly, in some instances (fig 2) changes in VT, Rf/VT ratio, or both, worsened when airway obstruction became clinically evident (severe FEV_1 decrease) indicating the reinforcing role of bronchoconstriction on changes in breathing pattern. Secondly, in patients with mild to moderate asthma increase in Rf along with decrease in VT during spontaneous breathing[13] may cause the VD/VT ratio to increase, and the ventilation-perfusion ratio to broaden; these abnormalities may result in a considerable fall in Pao_2.[13 18] We feel therefore that abnormalities in breathing pattern should be evaluated during bronchial provocation tests in order to anticipate potential ventilatory patterns associated with spontaneous asthmatic attacks.[13–18]

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