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Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre

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ABSTRACT Features of asthma include increases in both bronchial responsiveness and variability of airflow rates. We examined the relationship between bronchial responsiveness to histamine and the variation of peak expiratory flow rate (PFR) during the day and in response to salbutamol (200 μg), and the initial FEV_1 at the time of the histamine test and FEV_1 response to salbutamol. Bronchial responsiveness to histamine was expressed as the provocation concentration causing a fall in FEV_1 of 20% (PC_{20}). PC_{20} ranged between 13·9 and 130 mg/ml in nonasthmatic subjects, between 10·5 and 59·9 mg/ml in five asymptomatic asthmatics, and between 0·03 and 20·8 mg/ml in 27 asthmatics with symptoms controlled by medication. The lower the PC_{20} (the greater the bronchial responsiveness) the lower the morning PFR ($r = 0·79$), the greater the increase in PFR after salbutamol (morning $r = -0·75$, evening $r = -0·80$), and the greater the difference between the highest and lowest PFR each day ($r = -0·81$). Measurements of PFR were abnormal, compared with those in nonasthmatic subjects, in all subjects with a PC_{20} less than 2 mg/ml—that is, moderate or severe increase in nonspecific bronchial responsiveness—and in none with a PC_{20} greater than 21 mg/ml—that is, normal responsiveness; five of nine asthmatics with controlled symptoms had abnormal PFR measurements when PC_{20} was between 2 and 21 mg/ml—that is, mild hyperresponsiveness. In contrast, FEV_1 at the time of the histamine test was greater than 80% predicted in all subjects with a PC_{20} greater than 2 mg/ml and was not less than this in 10 of 18 subjects with a PC_{20} less than 2 mg/ml. When improvement in FEV_1 was 20% or more after salbutamol, the PC_{20} was usually moderately or severely increased (less than 0·4 mg/ml). The results identify a close relationship between nonspecific bronchial responsiveness to histamine and the variability in flow rates which occurs spontaneously and after bronchodilator. In addition, they raise the possibility that increased airflow obstruction in asthma may be a consequence of increased responsiveness.

Scadding[1] has simplified the definitions of asthma proposed by the Ciba Foundation Guest Symposium[2] and the Committee on Diagnostic Standards of the American Thoracic Society[3] to "a disease characterised by a wide variation over a short periods of time in resistance to flow in the airways of the lungs." Increases in resistance to airflow may occur spontaneously as in diurnal variation, may be induced by various nonspecific stimuli which affect asthmatics and by allergens, some industrial chemicals such as isocyanates, and non-steroid anti-inflammatory agents which only affect some asthmatics. Airway resistance may be reduced by treatment with drugs such as bronchodilators or corticosteroids.

Confirmation of the presence of asthma is usually made by improvement in FEV_1 after bronchodilator,[4] by measurements of diurnal variation of peak expiratory flow rate (PFR),[5 6] and by demonstration of an increase in bronchial responsiveness to nonspecific or allergic or other specific stimuli.[7] Nonspecific bronchial responsiveness is often measured by inhalation tests with histamine or methacholine,[8] and this correlates closely with

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responsiveness to other nonspecific stimuli such as exercise[9] and cold air.[10]

In this study we have examined, in nine nonasthmatic and 32 asthmatic subjects, the relationship between nonspecific bronchial responsiveness to histamine and the diurnal variation of PFR and the response to bronchodilator, the FEV_1 measured at the time of the histamine test, and the improvement in FEV produced by a bronchodilator.

Methods

Nine adults regarded as nonasthmatic were recruited from hospital staff (table). None had current or previous episodic dyspnoea, chest tightness, wheezing, or chronic cough. Two were current cigarette smokers and two others were atopic as indicated by one or more wheal and flare responses to prick skin tests with 16 common allergen extracts.

Thirty-two subjects considered to have asthma and no other chest disease were selected from patients attending the Chest and Allergy Clinic (table). All had a history of episodic dyspnoea and wheeze and relief of symptoms by treatment with a bronchodilator. Five had not had symptoms or required medication for six months to 10 years. The remaining 27 asthmatic subjects had current symptoms or were symptom-free on regular medication. Three were current smokers and 21 were atopic.

All 41 subjects were free of respiratory infection or exposure to allergen to which they were sensitised (except for house dust in 16) for four weeks before the study and during the study. Medication used by the 27 asthmatics was inhaled salbutamol less than once daily in nine and daily salbutamol in 18 with additional beclomethasone in 12 and additional prednisone in one. Salbutamol was withheld for at least six hours before measurement of peak expiratory flow rate (PFR) and bronchial responsiveness to histamine or salbutamol. At the time of the study, the initial FEV_1 was greater than 86% predicted in the nonasthmatics and greater than 91% predicted in the asthmatics without symptoms; in the asthmatics with current symptoms it was greater than 80% in 19 and 43–78% in other eight (table).

MEASUREMENT OF BRONCHIAL RESPONSIVENESS TO HISTAMINE

An inhalation test with histamine was carried out in each subject between 1200 and 1700h using the method described by Cockcroft *et al.*[11] First the subjects rested in the laboratory for 30 min and then their FEV_1 was measured. Then each inhaled an aerosol of saline followed by two-fold increasing concentrations of histamine acid phosphate (0·03–64 mg/ml). Aerosols were generated by a Wright nebuliser (airflow rate 7·5 l/min, pressure 50 lb/in^2 (344 kPa), output 0·145 ml/min) and inhaled by tidal breathing for 2 min. The response was measured by FEV_1 30 s and 90 s after each inhalation. Inhalations were discontinued when there was a fall in FEV_1 of 20% or more from the lowest post-saline value. The results were expressed as the concentration of histamine which caused a fall in FEV_1 of 20% (PC_{20}) and this was obtained from the log concentration-percent fall in FEV_1 curve by linear interpolation of the last two points. Concentrations of greater than 64 mg/ml were not used because of systemic side effects. If this concentration caused a fall in FEV_1 of 15–19% the PC_{20} was estimated by extrapolation of the concentration-response curve. Four nonasthmatic subjects were excluded because the fall in FEV_1 after this concentration was less than 15%.

MEASUREMENT OF PFR AND RESPONSE TO SALBUTAMOL

The subjects measured their PFR with a mini Wright peak flow meter twice daily (0600–0800h and 1600–1800h) for seven days after the histamine inhalation test. On each occasion the best of three blows was recorded before and 15 min after inhalation of salbutamol (200 μg) from a pressurised canister. Subjects kept a diary of their symptoms and treatment over this period.

On the day after completion of PFR measurements, at the same time of day as their PC_{20} was determined, the subjects returned to the laboratory and, after a rest of 30 min, their FEV_1 was measured before and 15 min after inhalation of salbutamol (200 μg).

ANALYSIS

Logarithmic transformation of PC_{20} was used for all calculations. From the four PFR results each day the percentage increase after bronchodilator morning and evening and diurnal variation of PFR was calculated. Diurnal variation was estimated from both the difference between the two pre-salbutamol results and the difference between the maximum and minimum PFR, and expressed as a percentage of the maximum value. The average of seven days' results was used for analysis. Predicted values for PFR were taken from Cherniack[12] and for FEV_1 from Morris *et al.*[13]

Linear regression analysis was used to examine the relationship between PC_{20} and PFR or FEV_1. If the relationship appeared non-linear, as for the increase in PFR after salbutamol, logarithmic transformation of both PC_{20} and PFR was used. A normal range for increase in PFR and FEV_1 after salbutamol and for diurnal variation in PFR was taken

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Table *Summary of details and results of test measurements in study subjects*

	Nonasthmatic	*Asthmatic*	
		Past History	*Current*
Number	9	5	27
Male	4	4	14
Age (yr)	32 (25–36)*	39 (35–52)	44 (21–67)
PC_{20} (mg/ml)	45 (13·9–130)	25·6 (10·4–60)	0·87 (0·03–20·8)
FEV_1 initial (% maximum)	94·2 (4·5)†	96·7 (3·4)	87·5 (11·7)
maximum (% predicted)	105·3 (8·5)	114·5 (9·9)	96·6 (17·5)
PFR maximum (% predicted)	106·9 (10·1)	105·2 (10·8)	94·5 (13·7)
diurnal variation (% maximum)			
without salbutamol	2·7 (1·7)	5·0 (3·9)	7·5 (5·9)
with salbutamol	6·7 (2·0)	8·0 (4·0)	21·9 (9·9)
Response to salbutamol (% increase)			
PFR 0600–0800	4·3 (2·4)	4·5 (2·3)	22·6 (14·9)
PFR 1600–1800	3·4 (1·5)	3·2 (1·4)	18·7 (18·1)
FEV_1	3·1 (2·7)	2·4 (1·6)	18·2 (18·8)

*mean (range)
†mean (SD)

as the 95% confidence interval for a single seven-day estimate about the mean of the nine nonasthmatic subjects.

Results

Bronchial responsiveness to histamine, expressed as PC_{20} (mg/ml), ranged between 13·9 and 130 in nonasthmatics, 10·5 and 59·9 in asymptomatic asthmatics, and 0·03 and 20·5 in asthmatics with current symptoms (table).

Bronchial responsiveness in each subject was related to the mean morning and evening PFR (expressed as a percent of maximum), the mean increase in morning and evening PFR after salbutamol, and the diurnal variation in PFR (figs 1–3). Strong correlations were observed between PC_{20} and PFR, increase in PFR after salbutamol, and diurnal variation using minimum pre-salbutamol and maximum post-salbutamol values. The lower the PC_{20} (the more increased the bronchial responsiveness) the lower the PFR in the morning ($r = 0·82$, $p < 0·001$) and evening ($r = 0·68$, $p < 0·001$) (fig 1), the greater the increase in PFR after salbutamol (morning $r = -0·75$, $p < 0·001$; evening $r = -0·80$, $p < 0·001$) (fig 2), and the greater the variability in PFR during the day ($r = -0·81$, $p < 0·001$) (fig 3B). A weaker correlation was observed between PC_{20} and diurnal variation of PFR using only the pre-salbutamol values ($r = -0·41$, $p < 0·01$) (fig 3A). Peak flow rate measurements were interpreted as abnormal if they were above the 95% confidence interval determined from the nonasthmatic subjects (figs 2, 3). When PC_{20} was less than 2 mg/ml all subjects (asthmatics with current symptoms) had abnormal values, when it was greater than 20·8 mg/ml the three symptom-free asthmatics had normal values, and when it was between 2 and 20·8 mg/ml six out of 12 subjects (five of nine asthmatics and one of two symptom-free asthmatics) had abnormal values.

Bronchial responsiveness in each subject was also related to the increase in FEV_1 after salbutamol measured one week after but at the same time of day as the histamine test (fig 4). The baseline FEV_1 was within 15% of FEV_1 on the day of the histamine test except in four subjects, higher in two, and lower in two (fig 4). When FEV_1 at the time of the histamine test was expressed as a percent of maximum, it was not abnormal until the PC_{20} was less than 0·4 mg/ml—that is, it could be normal when bronchial responsiveness was moderately to severely increased (fig 5). When the FEV_1 increased by 20% or more after salbutamol the PC_{20} was always less than 0·4 mg/ml—that is, bronchial responsiveness was moderately or severely increased.

Discussion

The results of this study demonstrate a strong association between the level of bronchial responsiveness to histamine and the degree of reduction in the morning PFR, the degree of improvement in morning PFR after salbutamol, and the diurnal variation of PFR as measured by the lowest pre-salbutamol value (usually on waking) and the highest post-salbutamol value (usually in the afternoon). The greater the bronchial responsiveness (the lower the PC_{20}) the lower the PFR, the greater the response to salbutamol, and the greater diurnal variation of flow rates. The study covered a wide range of PC_{20} and included asthmatic subjects with current symptoms, subjects with a past history of asthma, and normal subjects.

All subjects with a PC_{20} less than 2 mg/ml had a greater than normal variability of airflow obstruc-

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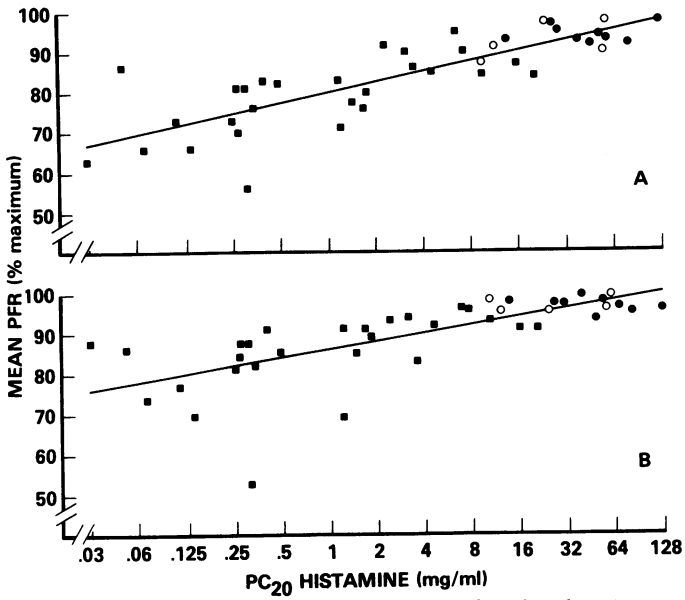

Fig 1 *Relationship between PC_{20} histamine (mg/ml) and peak expiratory flow rate (PFR) measured at 0600–0800h (A) (r = 0·82) and 1600–1800h (B) (r = 0·68). PFR is the mean of measurements on seven days and is expressed as a percentage of the maximum PFR each day. Forty-one subjects—nine nonasthmatic (●), five previous asthmatic (○), and 27 current asthmatics (■).*

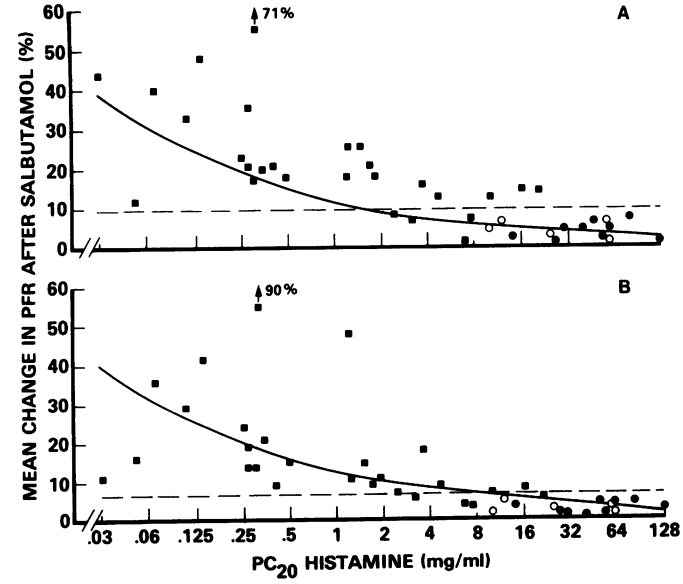

Fig 2 *Relationship between PC_{20} histamine (mg/ml) and response to salbutamol (200 μg), expressed as percentage increase in PFR. Response to salbutamol was measured at 0600–0800h (A) (r = −0·78) and 1600–1800h (B) (r = −0·80) for seven days. The horizontal line represents the upper bound of the 95% confidence interval about the mean of the nonasthmatic subjects; A, 9·9% and B, 6·6%. The curvilinear relationship was obtained by linear regression analysis using logarithmic transformation of both PC_{20} and change in PFR. Symbols as in fig 1.*

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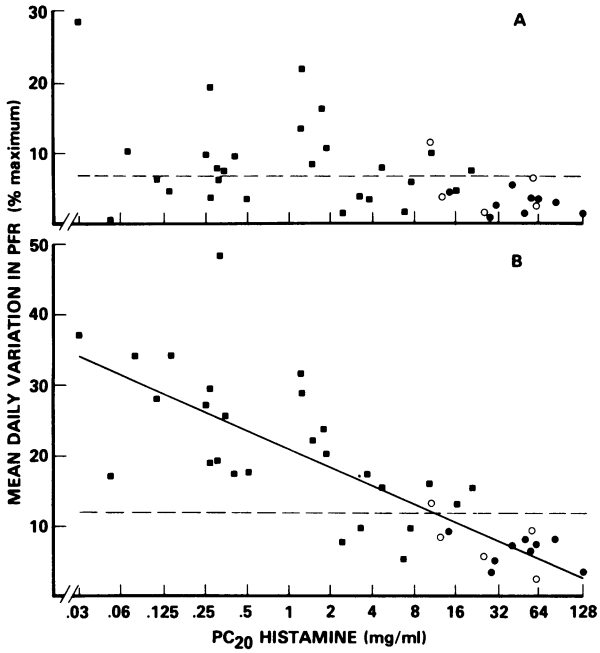

Fig 3 *Relationship between PC_{20} histamine (mg/ml) and variability of PFR during the day. PFR was measured before and after salbutamol at 0600–0800h and 1600–1800h. Variability was calculated by two methods: (A) the difference between the two PFRs before salbutamol and expressed as a percentage of the higher (r = −0·41) and (B) the difference between the maximum and minimum of the four PFR results each day and expressed as a percentage of the maximum (r = −0·81). The horizontal line represents the upper boundary of the 95% confidence interval about the mean of the nonasthmatic subjects; A 6·7% and B 11·8%. Symbols as in fig 1.*

tion, as indicated by measurements of diurnal fluctuation of PFR and response to bronchodilator, and were regarded as having asthma with current symptoms. When PC_{20} was greater than 20 mg/ml no subject had current symptoms of asthma or any increase in variability of PFR. Three subjects with previous symptoms of asthma had a PC_{20} above 20 mg/ml; this is to be expected since bronchoconstriction may be incited by a vigorous enough specific reaction stimulated by allergen[14] or chemical,[15] and nonspecific responsiveness may be increased so that the PC_{20} falls below 20 mg/ml by these[16 17] and other stimuli such as infection.[18]

In subjects with a PC_{20} from 2 to 20 mg/ml only about half of those with current symptoms showed increased variability of PFR. Subjects with this mild degree of responsiveness might have a greater perception of asthma[17] or have symptoms induced by various potent nonspecific stimuli. For example, exercise in warm air may induce bronchoconstriction in subjects with a PC_{20} histamine of up to 4 mg/ml[9] and isocapnic hyperventilation of cold dry air may induce bronchoconstriction in subjects with a PC_{20} of up to 16 mg/ml.[10] The observations in the present study are consistent with the findings of Juniper *et al*,[17] who reported that subjects with a PC_{20} of more than 2 mg/ml required either no treatment or bronchodilator taken only as required but not daily, indicating that they were not having reductions in flow rate of sufficient severity to cause troublesome symptoms. It is possible for apparently nonasthmatic people to have a PC_{20} in this range with an increase in variability of flow rates which they have not detected or regarded as abnormal.

The results of our study show that diurnal fluctuation of PFR of more than 12%, response to bronchodilator in the morning of more than 10%, and improvement in FEV_1 after bronchodilator of more than 10% is a greater than normal variation in flow rate and is suggestive of asthma. These results for PFR differ from those recorded by Hetzel and Clarke, who suggested that a diurnal variation of 20% was a useful screening test for asthma.[5] However, they studied asthmatics during or shortly after admission to hospital because of severe asthma and milder or more stable asthmatics may not demonstrate this degree of variability. Measurement of FEV_1 before and after bronchodilator at a clinic visit or estimation of diurnal variation without use of bronchodilator appeared less sensitive than measurement of diurnal variation recorded before and after bronchodilator. Obviously the usefulness of measurements of variability of flow rates for the diagnosis of asthma needs to be examined formally and compared with the usefulness of measurement of bronchial responsiveness to histamine or methacholine in a larger number of subjects who are carefully characterised by clinical features.[21]

The results also raise the question of the role of bronchial responsiveness in the pathogenesis of asthma; is hyperresponsiveness the primary abnormality in asthma and a prerequisite for the occurrence of airflow obstruction or is it a consequence of reduced airway calibre?[22 23] Our results show that asthmatics may have a moderate or severe increase in responsiveness (PC_{20} < 2·0 mg/ml) at a time when their FEV_1 is within 10% of maximum. Furthermore changes in airway resistance have been observed without changes in responsiveness,[24] and changes in responsiveness have been observed without changes in resistance.[16] These observations suggest that other factors are involved in increased responsiveness—for example, there may be an intrinsic abnormality in smooth muscle. In bronchial smooth muscle removed from sensitised and unsensitised dogs baseline tone was the same but the

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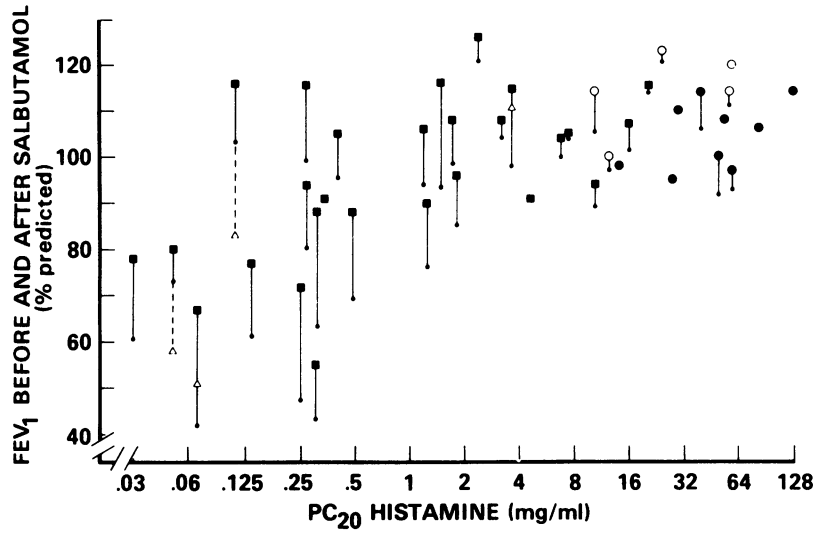

Fig 4 *Relationship between PC_{20} histamine (mg/ml) and FEV_1 as % predicted, measured before (·) and 15 minutes after inhaled salbutamol (200 μg). (● nonasthmatics, ○ previous asthmatics, ■ current asthmatics). If the FEV_1 before salbutamol was more than 10% different from the FEV_1 before the histamine inhalation test the latter is also shown (▽). When the difference was <2% only one symbol is shown.*

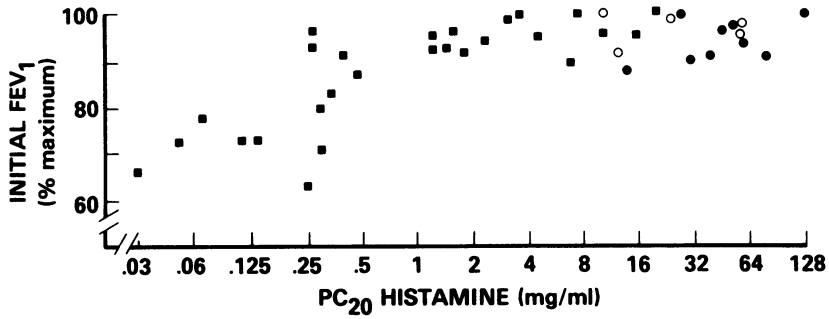

Fig 5 *Relationship between PC_{20} histamine (mg/ml) and initial FEV_1 at the time of the histamine inhalation test. FEV_1 is expressed as a percentage of maximum FEV_1 after inhaled salbutamol (200 μg) measured seven days later. Symbols as in fig 1.*

smooth muscle of the sensitised dogs was more hyperresponsive to carbachol.[25] It is therefore possible that bronchial responsiveness is the primary abnormality in asthma, which leads to the changes in smooth muscle tone and airway calibre.

Agreement has not been reached on the definition of asthma. Until there is more understanding of the causes and mechanisms of asthma a definition in terms of a disorder of function, such as that proposed by Scadding,[1] is most satisfactory. However, as illustrated in the present study, an increase in the variability in airflow rates may be difficult to confirm in mild asthma without provocation challenge procedures. Fortunately increased nonspecific bronchial responsiveness is present in virtually all subjects with current symptoms of asthma and the responses to different nonspecific stimuli seem to correlate quite closely.[9,10] Nonspecific responsiveness to histamine or methacholine can be easily measured[11] and normal responses to these agents and abnormal response to others such as exercise and cold air have not been observed.

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