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Ventilatory pattern during bronchial histamine challenge in asthmatics

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ABSTRACT: We wanted to investigate whether asthmatic subjects change their ventilatory pattern consistently when forced expiratory volume in one second (FEV_1) has declined by at least 20% during bronchial histamine challenge, in order to assess whether respiratory pattern analysis can be used to monitor bronchial obstruction continuously.

Histamine challenge was performed twice within a four week period, in eight asthmatic teenagers. Respiratory inductive plethysmography (RIP) was used for respiratory pattern evaluation, whilst the patients breathed on a mouthpiece attached to a pneumo-tachometer (PTM) whilst wearing a noseclip (first histamine challenge), and during natural breathing (second HiCh). End-tidal carbon dioxide tension (P_{ETCO_2}) was measured on both occasions.

During the second histamine challenge, four of the eight patients responded with a 72% (mean) increase in minute ventilation ($\dot{V}_E$), an 80% increase in mean inspiratory flow ($\dot{V}_I$), and a 20% decrease in P_{ETCO_2}. $\dot{V}_E$ and $\dot{V}_I$ were unchanged, or tended to decrease, among the other four patients (ventilatory nonresponders). Neither provocative dose producing a 20% fall in FEV_1 (PD_{20}) to histamine nor the magnitude of the fall in FEV_1 differed between ventilatory responders and nonresponders. The ventilatory response to inhaled histamine was abolished when breathing through a PTM.

Histamine induced bronchospasm is not uniformly reflected in the breathing pattern. Hyperventilation during histamine challenge might be the consequence of vagal airway receptor activation. Respiratory pattern analysis is not a feasible way to monitor bronchial obstruction during histamine challenge.

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Respiratory pattern analysis might offer a possible method for detecting or monitoring bronchial obstruction in situations (*e.g.* during sleep), and in subjects (*e.g.* infants), which do not permit standard lung function testing. Raised minute ventilation ($\dot{V}_E$) and mean inspiratory flow ($\dot{V}_I$) have been seen in subjects with obstructive airway disease [1–3], and during bronchial challenge [4].

It has been demonstrated that the use of a mouthpiece or a face mask during measurements of respiratory volumes induces changes in the respiratory pattern, *i.e.* tidal volume (V_T) and $\dot{V}_I$ increases whilst $\dot{V}_E$ is variably affected [5–7]. Such artifacts may conceal alterations of the natural respiratory pattern related to bronchial obstruction [4].

Respiratory inductive plethysmography (RIP) is a method for "noninvasive" ventilatory monitoring [8]. Under optimal conditions, respiratory volumes can be measured by RIP with an error of less than 10% [9].

RIP has been used for monitoring of the natural breathing pattern during induced bronchial obstruction in only a few studies [4, 10]. CHADHA *et al.* [4] observed a consistent increase in RIP derived $\dot{V}_I$ and $\dot{V}_E$ during progressive methacholine-induced bronchoconstriction in six healthy subjects. In a similar study on asthmatic subjects, STEWART *et al.* [10] found no such consistent increase in $\dot{V}_E$ or $\dot{V}_I$ during either histamine- or methacholine-induced bronchial obstruction. The RIP calibration and validation procedures used in the latter study were, however, simplified and differed from standard procedures [9], making data and conclusions from that study less reliable.

We undertook the present study to see if there are consistent changes in the ventilatory pattern during bronchial histamine challenge (HiCh) among asthmatics. The aim was also to see if breathing through a pneumotachometer (PTM) blunts a possible ventilatory response. If the natural breathing pattern changes predictably, RIP monitoring might offer an alternative way of monitoring bronchoconstriction during HiCh.

Methods

Eight asthmatic teenagers (six males and two females) underwent HiCh and concomitant ventilatory and end-tidal carbon dioxide tension (P_{ETCO_2}) monitoring in the

sitting position, on two occasions within a four week period. Their age was 14–19 yrs (mean 16 yrs), height 1.55–1.95 m (mean 1.75 m), and weight 37–83 kg (mean 62 kg).

The subjects had all been controlled for chronic bronchial asthma at the Paediatric Allergy Clinic at the University Hospital in Linköping for several years. The participants were familiar with the lung function laboratory, and had previously gone through bronchial challenge tests.

All participants were taking inhaled $beta_2$-agonists when required, and all but one were regularly taking inhaled sodium cromoglycate or inhaled steroids for asthma. Three subjects were taking antihistamines. The asthmatic disease was stable in all subjects, and none reported any respiratory tract infection within three weeks of the study.

$Beta_2$-agonists, inhaled steroids, and disodium cromoglycates were withheld at least 8 h prior to the challenge, and antihistamines were withheld for 72 h.

The study was approved by the Ethics Committee for Human Research at the Linköping University, and informed consent was given by the test subjects and their parents.

Respiratory inductive plethysmography (RIP)

RIP is a respiratory monitoring technique, by which the thoracic and abdominal volume contributions to each breath are assessed by measuring the rib cage and abdominal wall movements during breathing [8]. The RIP system comprises two elastic cloth bands, each incorporating an insulated electrical wire, an oscillator connected to each band, and a signal demodulator.

The bands are placed around the subject, encircling the rib cage and the abdomen, respectively. The analogue outputs from the demodulator are proportional to the rib cage and abdominal cross-sectional areas. In the present study, the RIP signals were calibrated against a PTM by use of our software, utilizing a linear model of the ventilatory system and the method of least squares fit to calculate the volume-motion coefficient for each band [11].

During RIP calibration the seated subjects voluntarily performed controlled tidal volume breathing. At first the subjects breathed predominantly with the rib cage, and then predominantly with the abdomen. Data were recorded in six subsequent 32 s episodes with each pattern of breathing. A 16 s sequence from each 32 s period of predominantly rib cage breathing was linked to a 16 s sequence of predominantly abdominal breathing. The volume-motion coefficients were calculated from these six combined data recordings and the means were further used [11].

RIP accuracy was validated by recording respiratory volumes with RIP and PTM simultaneously over one minute. The tidal volume error was calculated for each breath, using the mean error regardless sign as a measure of RIP accuracy.

RIP can be used in either AC or DC mode, the latter enabling measurements of changes in level of functional residual capacity (FRC) [4, 8]. Because of temperature-related stability problems in DC mode, we used RIP in AC mode, and FRC changes were not recorded.

Bronchial histamine challenge (HiCh) and test protocol

Each patient was challenged twice using RIP for ventilatory monitoring. During the first HiCh, the patients breathed on a mouthpiece attached to a PTM whilst wearing a noseclip, and during the second HiCh the patients were "noninvasively" monitored by RIP, *i.e.* using neither a mouthpiece to a PTM nor a noseclip. After arrival in the laboratory, FEV_1 was measured three times with a dry sealed spirometer (Vicatest 5®, Mijnhardts, The Netherlands). The test subjects were accepted for participation if their FEV_1 recordings were stable (≤5% varia-bility), and if FEV_1 was at least 65% of predicted [12].

After positioning the RIP bands and securing them from slippage with adhesive tape, RIP was calibrated using the method described above. RIP band positioning and calibration was repeated until an initial validation of RIP accuracy disclosed an error of less then 10%. This was generally accomplished within one repositioning of the bands.

RIP recording of breathing was performed during 5 min prior to the histamine challenge (presaline).

We used a dosimetric nebulizer (Spira Elektro 2; Respiratory Care Center, Hamenlinna, Finland) with an output of 7.1 $\mu l \cdot breath^{-1}$, giving aerosol particles with a mass median aerodynamic diameter of 1.6 μm [13, 14]. Initially, 12 breaths of 0.9% saline were inhaled. Two and 5 min later, FEV_1 was recorded. The FEV_1 value recorded after 2 min was utilized as a postsaline value. Nebulized histamine solutions (1.6 or 16 $mg \cdot ml^{-1}$) were inhaled every 6 min in two or threefold increasing doses until the FEV_1 2 min after histamine had declined by at least 20%. The starting dose of histamine was 11 μg in all subjects except one, who was known to be very sensitive to histamine. His starting dose was 2 μg of histamine. FEV_1 recordings were performed 2 and 5 min after each histamine inhalation. The accumulated dose of histamine causing a 20% reduction in FEV_1 ($PD_{20}Hi$) was interpolated. Mean $PD_{20}Hi$ for the group of patients was calculated after log transformation of data.

RIP recording of breathing was performed during all 5 min after each histamine inhalation. The validity of the RIP recordings was checked during the sixth minute after each inhalation.

P_{ETCO_2} was measured with a CO_2 analyser, using an infrared light absorption technique (Ametek CD-3A; Applied Electrochemistry Ametek, Inc., Thermox Instruments Division; Pa; USA). Expiratory gas was sampled *via* a tube entering a small hole in the PTM during the first HiCh. During the second HiCh, expiratory gas was sampled *via* a catheter, which had its tip placed at the nasal orifice.

Data analysis

The following respiratory pattern parameters were derived from the calibrated RIP rib cage and abdominal

sum signal: inspiratory tidal volume (V_{TI}); expiratory tidal volume (V_{TE}); respiratory frequency (f); minute ventilation ($\dot{V}_E$); inspiratory time/total cycle time (T_I/T_{TOT}); mean inspiratory flow ($\dot{V}_I$; $\dot{V}_I = V_{TI}/T_I$); rib cage fraction of V_{TE} (V_{RC}/V_{TE}); normalized V_{TE}, $\dot{V}_I$ and $\dot{V}_E$, *i.e.* divided by the predicted vital capacity (VC): (V_{TE}/VC pred; $\dot{V}_I$/VC pred; and $\dot{V}_E$/VC pred).

Median values of the parameters were calculated in intervals of one minute. Respiratory pattern data obtained from the fifth minute after each inhaled dose were related to the FEV_1 obtained 2 min after inhalation during each step in the provocation. During validation of the RIP recordings, V_{TE} from the RIP were compared to the V_{TE} obtained by PTM. The natural variation in $\dot{V}_E$ and $\dot{V}_I$ was analysed by calculating the coefficient of variation (CV) of the median values from each minute during presaline recordings.

Statistical evaluations

Considering the CV of $\dot{V}_E$ and $\dot{V}_I$ (see Results) and the error of RIP volumes (≤10%), we regarded a 25% change in either $\dot{V}_E$ or $\dot{V}_I$ as being significant. The subjects were classified as ventilatory responders if their $\dot{V}_E$ and $\dot{V}_I$ increased more than 25% during the second HiCh, or else as nonresponders (table 1).

We investigated eight asthmatic subjects with the null hypothesis H_0: ventilatory response is found in 50% of asthmatic subjects during HiCh; and the alternative hypothesis H_1: ventilatory response is found in 95% of asthmatic subjects during HiCh. H_0 was rejected if seven or eight of the eight subjects responded. The risk of falsely rejecting H_0 gives $p<0.04$ (binomial distribution; Type I error), and the risk of accepting H_0 if H_1 is true gives $p<0.06$ (Type II error).

The two-tailed Wilcoxon signed rank test was used for comparisons between presaline and postsaline data, and between postsaline and threshold dose data.

Data were also separately analysed for the ventilatory responders and the nonresponders. Groupwise comparisons between responders and nonresponders were performed using the Mann-Whitney U-test for postsaline and threshold dose data. $\dot{V}_E$ and $\dot{V}_I$ were not compared using threshold dose data, since these parameters were used for group classification.

The errors of RIP V_{TE} measurement obtained during postsaline validation and during histamine threshold dose validation were compared pairwise, using the two-tailed Student's t-test.

PD_{20}Hi from the first and the second HiCh were compared using the Wilcoxon signed rank test. A p-value of <0.05 was considered to be statistically significant.

Results

Second HiCh ("noninvasive" RIP monitoring)

Validation of RIP derived V_{TE} presaline disclosed an error of 3.6±2.7% (mean±SD), (range 0.8–7.490), post-saline error was 4.6±2.2%, (range 1.9–8.1%), and after the histamine threshold dose the error was 6.1±4.6%, (range 1.1–13.7%), for the eight subjects as a group. No significant differences in RIP accuracy were demonstrated between pre- and postsaline, or between postsaline and after histamine threshold dose.

Comparisons of pre- and postsaline data for all eight patients indicated no significant changes in the respiratory

Table 1. – Respiratory parameters from the second HiCh ("noninvasive" RIP monitoring)

	Postsaline					After histamine threshold dose				
	Responders n=4		Nonresponders n=4			Responders n=4		Nonresponders n=4		
FEV_1 % pred	88	(3)	87	(11)		65	(6)	63	(11)	
FEV_1 % baseline	100	-	100	-		73	(5)	74	(9)	
$\dot{V}_I$ $l \cdot s^{-1}$	0.35	(0.07)	0.31	(0.08)		0.63	(0.07)	0.26	(0.08)	a
$\dot{V}_E$ $l \cdot min^{-1}$	7.6	(0.8)	6.7	(1.9)		12.8	(2.1)	5.5	(1.5)	a
V_{TE} l	0.68	(0.12)	0.46	(0.07)	*	0.97	(0.28)	0.46	(0.11)	*
f $br \cdot min^{-1}$	11.4	(1.1)	14.9	(2.6)		14.0	(3.7)	11.7	(2.3)	
T_I/T_{TOT}	0.37	(0.04)	0.37	(0.03)		0.36	(0.08)	0.35	(0.04)	
P_{ETCO_2} kPa	5.08	(0.62)	5.60	(0.42)		4.05	(0.54)	5.33	(0.62)	*
V_{RC}/V_{TE} %	65.2	(14.1)	68.5	(10.3)		57.7	(30.5)	70.9	(12.8)	
$\dot{V}_I$/VC s^{-1}	0.070	(0.023)	0.078	(0.010)		0.123	(0.033)	0.068	(0.022)	a
$\dot{V}_E$/VC min^{-1}	1.49	(0.41)	1.70	(0.24)		2.46	(0.37)	1.41	(0.34)	a
$\dot{V}_{TE}$/VC	0.13	(0.05)	0.12	(0.02)		0.19	(0.08)	0.12	(0.03)	

Mean and (SD) of data from postsaline and histamine threshold dose RIP recordings are given for ventilatory responders and nonresponders. Statistical comparisons between responders and nonresponders were performed using the Mann-Whitney U-test for postsaline and threshold dose values, respectively. *: $p<0.05$; a: $\dot{V}_E$ and $\dot{V}_I$ were used to define responders and nonresponders and are, therefore, not compared groupwise for threshold data. HiCh: histamine challenge; RIP: respiratory inductive plethysmography; FEV_1: forced expiratory volume in one second; $\dot{V}_I$: inspiratory flow; $\dot{V}_E$: minute ventilation; V_{TE}: expiratory tidal volume; f: respiratory frequency; T_I/T_{TOT}: inspiratory time/total cycle time; P_{ETCO_2}: end-tidal carbon dioxide tension; V_{RC}/V_{TE}: rib cage fraction of V_{TE}; $\dot{V}_I$/VC, $\dot{V}_E$/VC and V_{TE}/VC: normalized $\dot{V}_I$, $\dot{V}_E$ and V_{TE}, respectively, *i.e.* divided by vital capacity.

parameters with the exception of a slight increase in V_{TE} and V_{RC}/V_{TE} at postsaline.

The CV for the presaline median values of $\dot{V}_E$ was in the range 3–17%, and the CV for $\dot{V}_I$ was in the range 2–16%.

Spirometric data from the recordings postsaline and from those after histamine threshold dose are given in table 1. Comparisons of post saline and histamine threshold dose data for all eight patients indicated no significant changes in the pattern of breathing. The P_{ETCO_2}, however, was significantly lowered for the whole group ($p<0.05$).

Four patients showed a significant increase (*i.e.* >25%) in $\dot{V}_E$ and $\dot{V}_I$ (responders) (table 1), whilst the other four slightly decreased their $\dot{V}_E$ and $\dot{V}_I$ (nonresponders). Comparing postsaline and threshold dose values, responders increased their mean $\dot{V}_I$ by 80% (range 68–108%), and their mean $\dot{V}_E$ by 72% (range 34–127%), and decreased their mean P_{ETCO_2} by 20% (range 11–29%). The nonresponders changed their mean $\dot{V}_I$ by -14% (range -36 to 9%), their mean $\dot{V}_E$ by -17% (range -32 to 3%), and their mean P_{ETCO_2} by -5% (range -10–0%). Among the responders there was a gradual and progressive change in $\dot{V}_E$, $\dot{V}_I$ and P_{ETCO_2} in relation to the FEV_1 decline (fig. 1a–c).

The responders and the nonresponders did not differ significantly as regards sex and age. However, the responders tended to be older, taller and heavier than the nonresponders (mean age 17 *vs* 15 yrs, mean height 1.84 *vs* 1.65 m, and mean weight 70 *vs* 54 kg). The relative FEV_1 decline after the histamine threshold dose was equivalent in the two groups (27 and 26%) (table 1). Mean $PD_{20}Hi$ was 77 μg (range 10–518 μg) among responders, and 221 μg (range 35–602 μg) among the nonresponders, showing no significant difference.

Postsaline FEV_1 % pred, $\dot{V}_I$, $\dot{V}_E$, *f*, T_I/T_{TOT}, normalized $\dot{V}_E$, normalized $\dot{V}_I$, and P_{ETCO_2} did not differ significantly between responders and nonresponders either (table 1).

V_{TE} was higher in responders than in nonresponders, both after saline inhalation and after histamine threshold dose ($p<0.05$) (table 1). V_{TE}/VC pred, however, showed no significant difference (table 1).

Threshold dose value for P_{ETCO_2} was significantly lower for responders than for nonresponders ($p<0.05$) (table 1).

First HiCh (breathing on a mouthpiece attached to a PTM, whilst wearing a noseclip)

No significant changes in the pattern of breathing were found when comparing postsaline and histamine threshold dose data for the whole group. The P_{ETCO_2} was, however, significantly lowered (5.40 *vs* 4.84 kPa). We compared $\dot{V}_E$ and $\dot{V}_I$ from the first and second HiCh during postsaline and histamine threshold dose for the responders. The increases in $\dot{V}_E$ and $\dot{V}_I$ recorded at the second HiCh were absent or blunted during the first HiCh (fig. 2). Only one subject markedly increased her $\dot{V}_E$ and $\dot{V}_I$ (a responder during the second HiCh); (fig. 2). Mean $PD_{20}Hi$ was 119 μg at the first HiCh, and 131 μg at the second HiCh (NS).

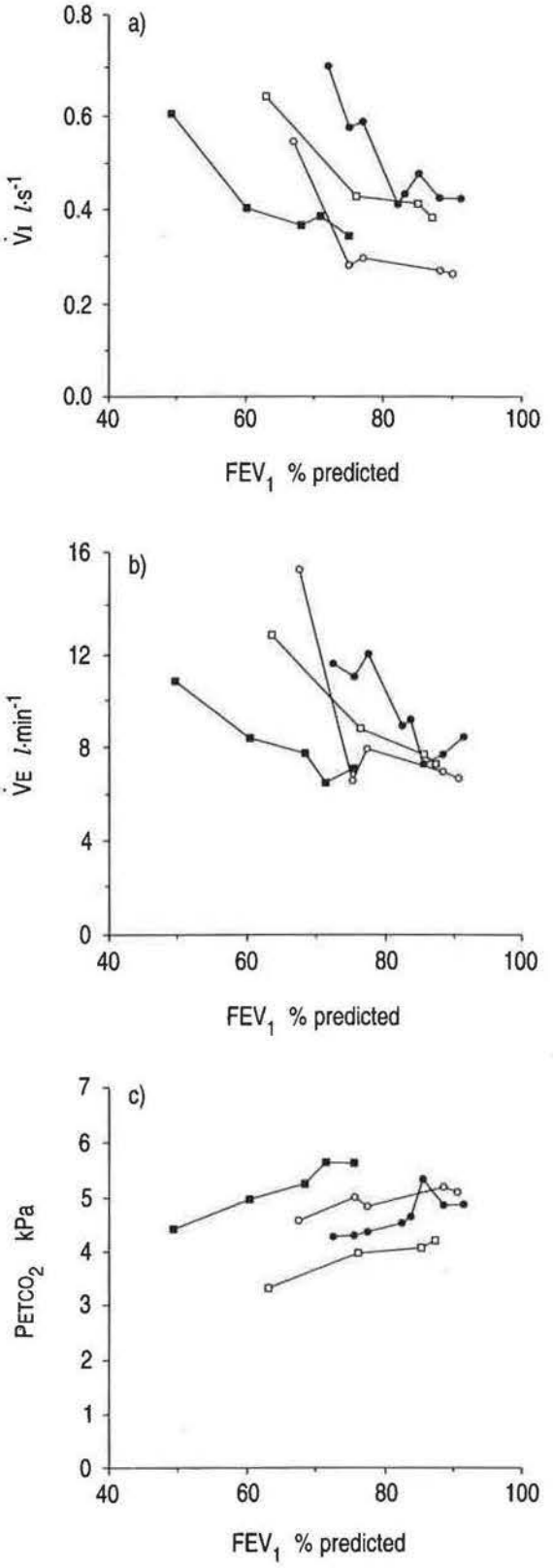

Fig. 1. – Mean inspiratory flow ($\dot{V}_I$) (a), minute ventilation ($\dot{V}_E$) (b), and end-tidal carbon dioxide tension (P_{ETCO_2}) (c), after saline inhalation (right hand point) and after each histamine dose during the second histamine challenge (HiCh) in relation to FEV_1 % predicted for ventilatory responders (n=4). Each line represents one patient. FEV_1: forced expiratory volume in one second.

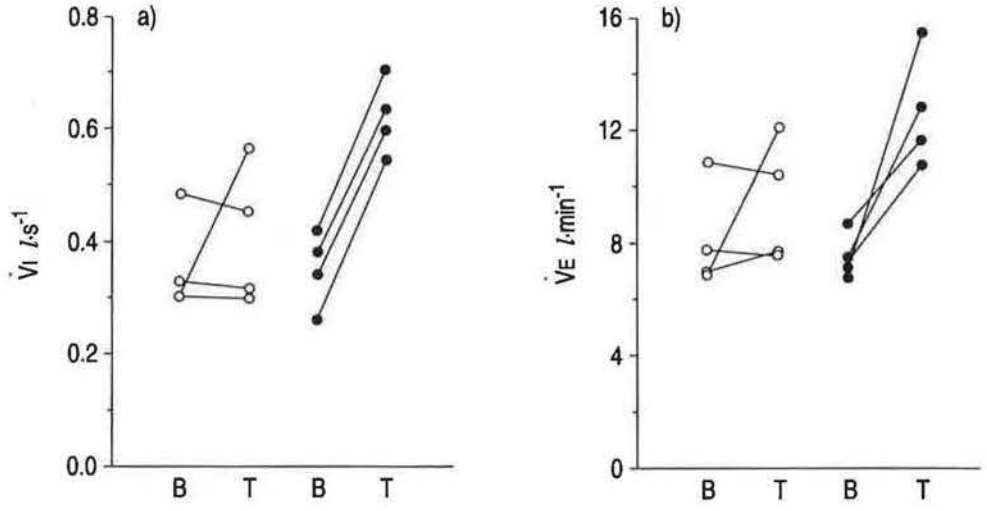

Fig. 2. – Mean inspiratory flow ($\dot{V}_I$) (a) and minute ventilation $\dot{V}_E$ (b) for ventilatory responders (n=4). Postsaline (B) and threshold dose (T) data during the first HiCh (mouthpiece breathing) (—○—) and during the second HiCh ("noninvasive" RIP monitoring) (—●—). HiCh: histamine challenge; RIP: respiratory inductive plethysmography.

Discussion

The present study showed that only four out of eight asthmatic subjects consistently increased their respiratory drive and ventilation during mild to moderate histamine induced bronchial obstruction. In addition, the study confirmed that breathing on a mouthpiece attached to a PTM, whilst wearing a noseclip blunts the breathing pattern response [4].

Half of the investigated patients responded with a significant increase (*i.e.* >25%) in $\dot{V}_I$ and $\dot{V}_E$, and with a decrease in P_{ETCO_2} after a 20% or more reduction in FEV_1 induced by histamine inhalation. The other four subjects (nonresponders) showed no such reaction, despite the induction of airway obstruction of the same severity. Only one subject markedly increased her $\dot{V}_E$ and $\dot{V}_I$ when using PTM during HiCh (fig. 2).

Our RIP calibration procedure [11] resulted in a high accuracy, both after saline and after the histamine threshold dose (mean errors 4.6 and 6.1%, respectively). The changes in $\dot{V}_E$ and $\dot{V}_I$ by far exceeded these errors, making RIP measurement errors a most unlikely explanation for the findings. Ventilatory responders and nonresponders did not differ as regards sex and age. Postsaline lung function values were similar. All subjects were familiar with the laboratory and with the lung function and bronchial reactivity testing.

CHADHA *et al.* [4] found no increases in $\dot{V}_E$ and $\dot{V}_I$ during methacholine-provoked obstruction when normal subjects breathed on a mouthpiece attached to a PTM, whilst using RIP on the same subjects gave consistent increases in $\dot{V}_E$ and $\dot{V}_I$. The use of a mouthpiece attached to a PTM changes ventilation due to irritation of the nasal and oral mucosa, by causing patient anxiety, and by increasing the respiratory dead space [5–7].

One possible explanation for the divergent ventilatory reactions is that different distributions of the constrictive reactions in the bronchial tree [15–18] underlie similar falls in FEV_1. The great increase in ventilation among responders could possibly be explained by a predominant peripheral airway obstruction, with an increased alveolar dead space ventilation [19] enhancing ventilation through chemoreceptor stimulation.

Different degrees of FRC elevation could be another cause of the heterogeneous response. Airway obstruction is commonly associated with an increased FRC [20], presumably to compensate for airway closure [21], and to reduce airway resistance [22]. The increase of FRC *per se* is believed to increase the ventilatory drive [23]. We did not use the RIP method to assess changes in FRC in the present study, as we have experienced that the drift of the RIP signals in the DC mode precludes reliable recordings.

Histamine can cause bronchoconstriction directly by stimulation of H_1 receptors on the bronchial smooth muscle, and indirectly through vagovagal reflexes [24]. In addition to its bronchoconstrictive effect, histamine may alter the respiratory pattern, probably by stimulation of vagal airway receptors [25–27]. The positive ventilatory response seen in half of the asthmatic subjects during HiCh was apparently out of proportion to the degree of bronchial obstruction and to homeostatic needs. The regulation of ventilation through chemoreceptor stimulation would attempt to keep arterial carbon dioxide tension (P_{ACO_2}) constant. The observed decrease in P_{ETCO_2} from 5.08 to 4.05 kPa among the responders during the "noninvasively" monitored HiCh (table 1), however, implies a much stronger stimulus of central respiratory drive. We suggest that vagal airway receptor activation caused the hyperventilation among the ventilatory responders.

MILLMAN *et al.* [25] used lidocaine anaesthesia to demonstrate the inhibition of the stimulatory effect on respiratory drive by inhaled histamine in normal subjects. The use of lidocaine in similar studies in asthmatics, however, is of limited use, since it has been shown that lidocaine causes bronchoconstriction in asthmatics [28].

In summary, the "noninvasively" assessed ventilatory response during histamine-induced bronchial obstruction

was highly variable in a group of asthmatic teenagers, despite equal FEV_1 reduction. Half of them responded with markedly increased minute ventilation and ventilatory drive, whilst minute ventilation was slightly decreased in the other subjects. Breathing on a mouthpiece abolished the response. We propose that the hyperventilatory response was caused by activation of vagal airway receptors, as it was excessive in relation to homeostatic demands. The study indicates that histamine-induced bronchospasm is not uniformly reflected in the breathing pattern. Respiratory pattern analysis does not appear to be an adequate method for airway obstruction monitoring during bronchial challenge.

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