Breathing pattern variability during bronchial histamine and methacholine challenges in asthmatics

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Breathing pattern variability was determined in 10 asthmatic adolescents during repeated bronchial histamine and methacholine challenges (HiCh/McCh). The purpose was to provide information on ventilatory control in asthmatics by comparing the variability of the various breathing pattern parameters at rest and during induced bronchial obstruction. Changes in variability during bronchial obstruction might be explained by either anxiety effects causing increased variability or by the minimization of the work of breathing causing decreased variability. Ventilation was monitored by respiratory inductive plethysmography in order to minimize the effects on the spontaneous pattern of breathing. Breath-to-breath and day-to-day variability were determined concerning respiratory frequency ($f_p$), inspiratory tidal volume ($V_{in}$), inspiratory ventilation ($V_{in}$), inspiratory time to total cycle time ratio ($T_{i}/T_{tot}$), mean inspiratory flow ($V_{i}/T_i$), an index of ventilatory drive), rib cage fraction of $V_{in}$ ($V_{rc}/V_{in}$), and maximum compartmental amplitude to $V_{in}$ ratio ($MCA/V_{in}$; an index of rib cage and abdominal phasing).

No difference in any parameter was found regarding breath-to-breath coefficient of variation ($CV=SD/mean$) between recordings at baseline, after saline inhalation and after threshold dose of the provocative agents, i.e. >20% fall in FEV$_1$. Variability was less for $MCA/V_{in}$ and $V_{rc}/V_{in}$ (mean CV 1.3 and 7.7%, respectively) than for $T_{i}/T_{tot}$, $f_{rc}$, $V_{in}/T_{in}$, $V_{in}$, and $V_{i}$ (14.2, 15.8, 20.9, 22.2 and 21.1%, respectively) ($P<0.01$). Likewise, the day-to-day variability did not differ in any parameter between recordings at baseline, after saline inhalation and after threshold dose. The variability was less for $MCA/V_{in}$ (0.7%) than for $T_{i}/T_{tot}$, $V_{rc}/V_{tp}$, $V_{in}$, $V_{rc}/T_{rc}$, $f_{rc}$, and $V_{in}$ (7.1, 12.1, 12.8, 14.2, 13.0 and 15.4%) ($P<0.05$). Furthermore, $T_{i}/T_{tot}$ was less variable than $V_{in}$ ($P<0.05$).

Thus, the ventilatory pattern was quite reproducible on a day-to-day basis, despite considerable breath-to-breath variability. Ventilatory drive and tidal volumes were more variable than the rib cage and abdominal phasing, the respiratory timing and the rib cage fraction of tidal volume. The lack of difference in variability between rest and induced bronchial obstruction indicates that other factors than anxiety or minimization of the work of breathing are important for the control of respiration in asthmatics during bronchial challenge.

Introduction

The mean ventilatory response during induction or reversal of bronchial obstruction has been dealt with in several papers (1–12), but the breath-to-breath and the day-to-day variability of this response have been minimally studied (13–14). The ventilatory responses to non-specific bronchial challenge have been assessed in several studies using either a spirometer (12) or a pneumotachometer (PTM) for ventilatory measurements (4, 6–7). However, breathing through a mouthpiece with the nose occluded changes the natural pattern of breathing, the tidal volume ($V_{t}$) and the mean inspiratory flow ($V_{i}/T_{i}$) increase and ventilation is variably changed (15–18). The use of respiratory inductive plethysmography (RIP) enables accurate indirect assessment of the spontaneous breathing pattern (1, 19–21).

The present authors (9, 22) and others (1,8) have studied the ventilatory response to induced bronchial obstruction in asthmatics. In the author’s first RIP study, four of eight patients had a marked increase in minute ventilation ($V_{e}$; 72% increase) and in $V_{i}/T_{i}$ (80% increase) to histamine, despite the lack of a significant change for the whole group (9). However, in the second study, also undertaken in asthmatic adolescents, the mean ventilatory response at the group level was a significant rise in $V_{i}/T_{i}$ (21%) and...
V'\textsubscript{t} (21 and 23%, respectively) during repeated bronchial histamine and methacholine challenge (HiCh and MeCh). The ventilatory response displayed considerable inter- and intra-individual variability (22). One reason for the slightly different results between these studies might be the day-to-day variability in the breathing pattern.

Tobin et al. investigated the variability of breathing pattern on a breath-to-breath and day-to-day basis in health subjects. They found that indices of respiratory timing were more constant than indices of ventilatory drive and the ventilatory sensitivity to CO\textsubscript{2} (14). Among healthy subjects, it has been shown that external resistive loading decreases variability in respiratory frequency (f\textsubscript{R}), in V'\textsubscript{t}, and in V'\textsubscript{t}/T\textsubscript{R}. This can be explained by mechanisms for minimization of the work of breathing (23). Furthermore, Kuratomi et al. found that the V'\textsubscript{t} variability (coefficient of variation; CV\textsubscript{V}) was 36% during an asthma attack and decreased to 22% after treatment (24).

The variability of the respiratory pattern in asthmatic patients has not been documented [except for V'\textsubscript{V} variability by Kuratomi et al. (24)], neither at baseline nor during induced obstruction. In order to form valid conclusions about changes in the respiratory pattern (9, 22), it is essential to know the variability of breathing pattern parameters in asthmatics both on a breath-to-breath and on a day-to-day basis.

The aim of the present study was therefore to determine the variability of the breathing pattern at baseline and when bronchial obstruction was induced by histamine and methacholine inhalation in asthmatic adolescents. Furthermore, the authors wanted to study whether the variability after induced bronchial obstruction decreases, as found by Daubenspeck during external resistive loading (23), or if the variability increases as found by Kuratomi et al. during acute asthma (24). The physiological mechanisms governing the respiratory control system might then be explained either in terms of minimization of the work of breathing (decreased variability) or by anxiety effects (increased variability).

**Methods**

**Patients**

Ten asthmatic adolescents (nine males and one female) underwent repeated HiCh and MeCh, and a single-blinded HiCh after \(\beta\textsubscript{2}\)-agonist pre-treatment at the same time of the day ± 2 h within a 4-month period. Their ages were between 15 and 21 years (mean 18 years), their heights were between 164 and 196 cm (mean 180 cm), their weights were between 46 and 87 kg (mean 68 kg), and their FEV\textsubscript{1} was between 78 and 106% (mean 92%) of predicted (25).

The patients had all been controlled for several years for chronic mild to moderately severe bronchial asthma at the Pediatric and Adolescent Allergy Clinic at the University Hospital in Linköping, Sweden. They were all familiar with the lung function laboratory and had previously undergone bronchial challenge tests. As most of the patients were seasonal allergies, tests were performed during the allergic off-season.

All patients were taking inhaled \(\beta\textsubscript{2}\)-agonists when required, and all but one were regularly taking inhaled sodium cromoglycate or inhaled corticosteroids for asthma. Three patients were taking oral antihistamines. The asthmatic disease was stable in all subjects and none reported any respiratory tract infection within 3 weeks of the study days.

Medication was kept constant during the investigation but \(\beta\textsubscript{2}\)-antagonists were withheld at least 8 h (short-acting agonists) and at least 24 h (long-acting agonists) prior to the challenge, and antihistamines were withheld for 72 h.

**Ethics**

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

**Technical Equipment**

Respiratory inductive plethysmography (RIP) was used for indirect ventilatory monitoring. The commercially available RIP device (Respitrace\textsuperscript{reg}®, Ambulatory Monitoring, NY, U.S.A.), consists of a demodulator, an oscillator and two wired elastic cloth bands encircling the rib cage and the abdomen, respectively. The thoracic and abdominal volume contributions to each breath are measured through the rib cage and the abdominal wall motions during breathing (26). These motions are translated into lung volume changes through volume-motion coefficients which are obtained during RIP calibration (26). In the present study, the RIP signals were calibrated against a PTM by means of the authors' software, utilizing either a linear model or, when improving accuracy, a non-linear model of the second degree of the ventilatory system and a least squares fit to calculate the volume-motion coefficient for the rib cage and the abdominal bands (20). Respiratory inductive plethysmography accuracy was validated by recording respiratory volumes with RIP and PTM simultaneously over 1 min. The tidal volume error was calculated for each breath, using the
mean error regardless of the sign as a measure of RIP accuracy.

A pneumotachometric spirometer (Flowscreen®, Jaeger, FRG) was used to measure FEV₁. Ventilation distribution and trapped gas measurements were assessed using a previously described computerized pneumotachometric multiple breath nitrogen washout method (27). The volume of trapped gas during nitrogen washout (VTGₐ₂) was measured as the volume of nitrogen expressed as the volume of air mobilized from previously non-ventilated lung spaces by five maximal breaths taken after a multiple breath nitrogen washout by tidal O₂ breathing, until the end-tidal nitrogen fraction was 0.02. As VTGₐ₂ is directly related to lung size in normal subjects, the percentage VTGₐ₂/VC can be used for inter-individual comparisons (27). Ventilation inhomogeneity was represented by the lung clearance index (LCI=WoV/FRC; WoV=washout volume) (28).

This study used an inhalation synchronized dosimetric nebulizer (Spira Elektro 2®, Respiratory Care Center, Hamenlinna, Finland), giving aerosol particles with a mass median aerodynamic diameter of 1.6 μm (geometric SD: 1.4 μm) (29,30). With a 0.5-s nebulization period, the output is 7.1~1 breath⁻¹ (29). The patients performed controlled tidal breathing through a mouthpiece wearing a noseclip. The inspiratory flow rate reached but did not exceed 0.5 l s⁻¹, as measured by the Spira flow indicator. After threshold dose measurements, the obstruction was relieved by inhalation of four doses of 0.1 mg salbutamol from a metered dose inhaler via a spacer (Volumatic®, Glaxo, U.K.).

**Protocol**

**Experiment 1**

Each patient was challenged on five separate days within a 4-month period. Both HiCh and MeCh were undertaken on two occasions. In addition, a HiCh was performed after a single-blinded inhalation of a β₂-agonist (four doses of 0.25 mg terbutaline from the Turbuhaler®, Astra, Sweden). Each challenge started with a VTGₐ₂ measurement followed by three FEV₁ recordings. The patients were accepted for participation if their FEV₁ recordings were stable on the study day (≤5% variability of baseline FEV₁), and if FEV₁ was at least 65% of predicted (25). Initially, 12 breaths of 0.9% saline were inhaled. Nebulized histamine or methacholine solutions (1.6 mg ml⁻¹ or 16 mg ml⁻¹) were then inhaled every 5 min in increasing dose until the FEV₁ recorded 5 min after the dose had declined by at least 20% (threshold dose). FEV₁ and SaₐO₂ (Sirecust MicroO₂®, Siemens AG; FRG) were recorded 5 min after each provocation dose. The volume of trapped gas during nitrogen washout was measured after threshold dose and 10 min after salbutamol inhalations. Dyspnoea was scored by the patients (0–10 points) by means of a modified Borg scale (31) immediately before the post-saline FEV₁ recordings, after threshold dose and 10 min after salbutamol inhalation. Respiratory inductive plethysmography recordings were undertaken over 3 min after saline and for 3 min immediately after each provocation dose. Data from the last 1.5 min of each RIP recording were evaluated. The validity of the RIP recordings was checked during the fourth minute after every second dose step, and after the threshold dose (see below). The choice of the 1.5-min recording period was made because of the transient nature of the histamine-induced bronchial obstruction. Cartier et al. showed that the peak obstructive response occurred at 1.6 min after inhalation of histamine and that the individual plateau may last for as short a period as 4 min (32).

**Experiment 2**

As FEV₁ manoeuvres could influence bronchial tone (33,34), the possible effect of forced expiratory manoeuvres on the breathing pattern variability, and the appropriate time interval for RIP ventilatory pattern recording after inhalation of the provocative agent were assessed. For this purpose, five patients participating in the actual study additionally underwent MeCh twice within 1 week. An FEV₁ measurement was taken after each dose step in the first MeCh. During the second MeCh, FEV₁ was measured only at baseline and after the last dose of methacholine, which was either the same dose as during the first MeCh or a lower one if the patient reported severe symptoms of bronchial obstruction. The VTGₐ₂ was measured, and dyspnoea was scored initially and after the last methacholine dose. Breathing pattern was monitored for 15 min after saline inhalation and after the threshold dose. Ventilatory parameters from the second MeCh were evaluated from data collected 1.5-3 min after inhalation (as above), and from data collected for 15 min. The effect of using a non-linear model of the ventilatory system for RIP calibration was assessed by calculating ventilatory parameters during the second MeCh by using both a linear model and a non-linear model of the ventilatory system.

**Experiment 3**

The effect on the breath-to-breath variability of respiratory pattern parameters from breathing through a PTM was tested at baseline in seven
asthmatic subjects. They breathed for 5 min without any connection to the mouth, and for 5 min through a mouthpiece connected to a pneumotachograph with a total deadspace of 48 ml, using a noseclip. Breathing pattern was analysed for 3–4 min during natural and deadspace loaded breathing, respectively.

DATA ANALYSIS

The following respiratory pattern parameters were derived from the calibrated RIP rib cage and abdominal sum signal: inspiratory tidal volume \( (V_{r,i}) \), respiratory frequency \( (f_R) \), inspiratory ventilation \( (V_i') \), inspiratory time/total cycle time \( (T_i/T_{to}) \), mean inspiratory flow \( (V_{r,i}/T_i) \), rib cage fraction of \( V_{r,i} \) \( (V_{rc}/V_{r,i}) \), maximum compartmental amplitude \( (MCA=\text{arithmetic sum of maximum amplitudes of RC and ABD during the breathing cycle, MCA}/V_{r,i}=1 \text{ if RC and ABD are in phase}) \).

Body movement may cause artifactual breath detection. Such artifacts were manually excluded. During validation of RIP accuracy, \( V_{r,i} \) recorded by the RIP \( (V_{r,i,\text{RIP}}) \) was compared to \( V_{r,i} \) obtained by the PTM \( (V_{r,i,\text{PTM}}) \); \( V_{r,i,\text{error}}=100(V_{r,i,\text{RIP}}-V_{r,i,\text{PTM}})/V_{r,i,\text{PTM}} \). If the \( V_{r,i} \) error from any of the validations after calibration, after saline inhalation, and after threshold dose exceeded 15%, or if the maximum change in error between these three validations exceeded 16%, data from that challenge were excluded. Furthermore, if \( FEV_1 \) fell more than 10% during HiCh with \( \beta_2 \)-agonist pre-treatment, pre-treatment data were not analysed. Data for all patients are presented as mean ± SD.

STATISTICAL CONSIDERATIONS

The variability for each breathing pattern parameter was assessed as the coefficient of variation \( (CV=sd/\text{mean}) \). The statistical distribution of the CV data was tested by the Shapiro–Wilks \( W \)-test for normality (35). The distributions of the breath-by-breath CV for \( V_{r,i}, V_{r,i}'/T_{r}, \) and MCA/\( V_{r,i} \), diverged from Gaussian but the logarithmically transformed equivalents did not. Therefore, statistical comparisons were carried out on log transformed CV. As changes in the mean values of the breathing pattern parameters may mask changes in the absolute values of the variability, the day-to-day variability was compared using both CV and absolute values (sd of a breathing pattern parameter) as measures of variability. Since the statistical comparisons gave similar results irrespective of using CV or SD as measures of variability, the CV was analysed.

Comparisons between the variability of the various breathing pattern parameters were made using the ANOVA F-test. Duncan’s multiple range test was used for comparisons between the variability of the different parameters (36). The Student’s t-test was used for comparing the variability at baseline and after saline inhalation, and the variability after saline inhalation and after threshold dose. A P-value less than 0.05 was considered statistically significant.

Results

In Experiment 1, data were excluded due to RIP inaccuracy in one case during the second HiCh, one case during the second MeCh, and one case during HiCh with \( \beta_2 \)-agonist pre-treatment. Two patients did not complete the second MeCh. During HiCh with \( \beta_2 \)-agonist pre-treatment, \( FEV_1 \) fell more than 10% in one subject and data were therefore excluded.

EXPERIMENT 1

The errors of \( V_{r,i} \) as measured by RIP (in comparison with \( V_{r,i} \) by a PTM) were \( 4.4\pm3.0\% \) at baseline, \( 4.7\pm3.5\% \) after saline, and \( 5.3\pm3.1\% \) after threshold dose (means for all five challenges). The breath-to-breath intra-individual variability of the breathing pattern parameters from the first HiCh and the first MeCh are presented in Table 1. There were no significant differences between the variability at baseline and that after saline inhalation for any parameter. The variability after saline inhalation and after threshold dose did not differ for any parameter except for MCA/\( V_{r,i} \). The mean values of the breath-to-breath variability differed significantly between the various breathing pattern parameters at baseline, after saline inhalation, and after threshold dose during the first HiCh and during the first MeCh \( (P<0.001 \text{ at baseline, after saline, and after threshold dose during both HiCh and MeCh; ANOVA } F \text{-test}) \). The average order of the variability (%) after saline and after threshold dose during HiCh and MeCh, moving from the least to the most variable parameter was: MCA/\( V_{r,i} \), \( V_{r,i}'/T_{r} \), \( f_R \), \( V_{r,i}/T_{r} \), \( V_{r,i} \), and \( V_{r,i}' \). The baseline variability was significantly less in MCA/\( V_{r,i} \) than in the other parameters, and significantly less in \( V_{r,i}'/V_{r,i} \) than in \( T_{r}/T_{to} \), \( f_R \), \( V_{r,i}/T_{r} \), and \( V_{r,i}' \), during both HiCh and MeCh \( (P<0.05; \text{Duncan’s multiple range test}) \).

The lung function parameters and the mean values of the breathing pattern parameters after saline inhalation and after threshold dose during the first HiCh and MeCh are given in Table 2. A detailed presentation of the changes in the mean values of the breathing pattern parameters based on repeated HiCh and MeCh is given elsewhere (22). The mean
Table 1  Breath-to-breath intra-individual variability (CV%) in breathing pattern parameters recorded by respiratory inductive plethysmography in 10 asthmatic patients during bronchial challenge

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Saline</th>
<th>Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HiCh</td>
<td>MeCh</td>
<td>HiCh</td>
</tr>
<tr>
<td>( f_R )</td>
<td>( 14.2 (4.5) )</td>
<td>( 16.8 (10.6) )</td>
<td>( 15.8 (5.3) )</td>
</tr>
<tr>
<td>( V_{ti} )</td>
<td>( 21.4 (8.5) )</td>
<td>( 19.0 (7.8) )</td>
<td>( 22.1 (10.1) )</td>
</tr>
<tr>
<td>( T' )</td>
<td>( 20.1 (9.5) )</td>
<td>( 21.6 (8.9) )</td>
<td>( 21.1 (7.7) )</td>
</tr>
<tr>
<td>( T'/T_{TOT} )</td>
<td>( 14.7 (5.2) )</td>
<td>( 14.7 (7.0) )</td>
<td>( 14.2 (5.3) )</td>
</tr>
<tr>
<td>( V_{s/c}/V_{tn} )</td>
<td>( 8.7 (3.9) )</td>
<td>( 9.4 (8.5) )</td>
<td>( 7.7 (4.7) )</td>
</tr>
<tr>
<td>MCA/V_{tn}</td>
<td>( 1.3 (1.7) )</td>
<td>( 0.8 (0.7) )</td>
<td>( 1.3 (2.1) )</td>
</tr>
</tbody>
</table>

Values are means (SD) expressed as percent. The data were derived from individual coefficients of variation (CV%) for each parameter in each of the 10 asthmatic patients during the first bronchial challenge with histamine (HiCh) and with methacholine (MeCh). Data are given at baseline, after saline inhalation, and after the threshold provocative dose, i.e. when FEV\(_1\) had declined at least 20% from baseline. \( f_R \), respiratory frequency; \( V_{ti} \), tidal inspiratory volume; \( V' \), inspiratory ventilation; \( T'/T_{TOT} \), inspiratory time/total cycle time; \( V_{s/c}/V_{tn} \), mean inspiratory flow; \( V_{s/c}/V_{tn} \), percentage rib cage contribution to \( V' \), ratio; MCA/V_{tn}, maximum compartmental amplitude to \( V' \), ratio. Statistical comparisons using the Student's t-test on log transformed data between baseline and saline values, and between baseline and threshold dose values. *P<0.05.

Table 2  Lung function and breathing pattern parameters during the first bronchial challenges with histamine (HiCh) and with methacholine (MeCh) in 10 asthmatic patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saline</th>
<th>Threshold dose</th>
<th>Saline</th>
<th>Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_R ) (1 min(^{-1}))</td>
<td>14.1 (2.7)</td>
<td>14.5 (5.4)</td>
<td>14.9 (3.3)</td>
<td>13.9 (2.1)</td>
</tr>
<tr>
<td>( V_{ti} ) (l)</td>
<td>0.62 (0.19)</td>
<td>0.77 (0.28)</td>
<td>0.67 (0.26)</td>
<td>0.79 (0.26)</td>
</tr>
<tr>
<td>( T'/T_{TOT} )</td>
<td>8.2 (1.5)</td>
<td>10.2 (2.4)</td>
<td>9.2 (2.3)</td>
<td>10.6 (2.9)</td>
</tr>
<tr>
<td>( V_{s/c}/V_{tn} ) (1 s(^{-1}))</td>
<td>0.38 (0.09)</td>
<td>0.46 (0.11)</td>
<td>0.44 (0.16)</td>
<td>0.48 (0.13)</td>
</tr>
<tr>
<td>MCA/V_{tn} (%)</td>
<td>67 (19)</td>
<td>78 (22)</td>
<td>69 (20)</td>
<td>70 (23)</td>
</tr>
<tr>
<td>MCA/V_{tn} (%)</td>
<td>1.01 (0.01)</td>
<td>1.03 (0.06)</td>
<td>1.02 (0.02)</td>
<td>1.02 (0.03)</td>
</tr>
</tbody>
</table>

Data are means (SD) obtained after saline and after threshold dose. See Table 1 for a definition of abbreviations.

The individual day-to-day variability is given in Fig. 1. There was no significant difference between the variability at baseline and after saline, nor between post-saline and threshold dose variability for any of the parameters, except for \( f_R \) being more variable at baseline than after saline (P<0.05; Student's t-test on log transformed CV). The mean values of the day-to-day variability differed significantly between the various breathing pattern parameters at baseline, after saline inhalation, and after HiCh and MeCh threshold dose (P<0.001 at baseline, after saline, and after HiCh and MeCh threshold dose; ANOVA F-test). The average order of the mean CV% at baseline, after saline, and after threshold dose during HiCh and MeCh, moving from the least to the most variable parameter, was: MCA/V_{tn} (0.7 ± 0.8), \( T'/T_{TOT} \) (7.1 ± 4.9), \( V_{s/c}/V_{tn} \) (12.1 ± 6.6), \( V' \), (12.8 ± 5.5), \( V_{s/c}/V_{tn} \) (14.2 ± 5.9), \( f_R \) (13.0 ± 6.8), \( V_{tn} \) (15.4 ± 6.5) (values in parentheses refer to recordings after saline inhalation). The variability was significantly less in MCA/V_{tn} than in the other parameters, and significantly less in \( T'/T_{TOT} \).
Fig 1 Day-to-day intra-individual variation in breathing pattern parameters. Coefficient of variation (CV%) of mean values for each parameter in each subject during the two bronchial challenges with histamine (HiCh), during the HiCh with β2-agonist pre-treatment, and during the two challenges with methacholine (MeCh). Data are given at baseline (a, CV of five mean values), after saline inhalation (b, CV of four mean values), after HiCh, (c) MeCh, (d) threshold dose, i.e. when FEV₁ had declined at least 20% (c,d, CV of two mean values, respectively).

than in \( f_R \) and \( V'_T \) \((P<0.05\); Duncan’s multiple range test).

EXPERIMENT 2

Although the numerical values of the variability differed between the 1.5- and the 15-min time intervals, the orders of the variability were similar, although not identical (Table 3). The mean values of the breath-to-breath variability significantly differed between the various breathing pattern parameters both after saline inhalation and after threshold dose during the second MeCh using either 1.5- or 15-min intervals \((P<0.001; \text{ANOVA } F\text{-test})\). The rank order for the CV, moving from the least to the most variable parameter, after saline inhalation was: MCA/\( V_T \), \( V_{TC}/V_T \), \( V_{TT}/T_T \), \( f_R \), \( T/T_{TOT} \), \( V'_T \), and \( V_Tr \) (Table 3). The variability was less in MCA/\( V_T \) than in the other parameters \((P<0.05; \text{Duncan’s multiple range test})\).

The average descending rank order for the CV’s after threshold dose was: MCA/\( V_T \), \( V_{TC}/V_T \), \( T/T_{TOT} \), \( f_R \), \( V'_T \), \( V_Tr \), and \( V'_T \) (Table 3). The variability was significantly higher for the 15-min interval than for the 1.5-min interval at baseline for \( V'_T \) \((P<0.05; \text{Table 3})\), and after threshold dose for \( f_R \) \((P<0.01)\) and for \( T/T_{TOT} \), \( V_{TC}/V_T \) and MCA/\( V_T \) \((P<0.05; \text{Table 3})\).

The CV for 15-min intervals was calculated using both a linear and a non-linear model of the respiratory system. The difference between the CV by either model was ≤3% for all parameters at baseline and after threshold dose. Hence, the use of a
Breathing pattern variability

Table 3  Breath-to-breath intra-individual variability (CV%) in breathing pattern parameters calculated from 1.5-min and 15-min intervals during methacholine challenge in five asthmatic patients

<table>
<thead>
<tr>
<th>Interval</th>
<th>Saline Threshold dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 min</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>$f_R$</td>
<td>24.7 (11.5)</td>
</tr>
<tr>
<td>$V_{ti}$</td>
<td>24.9 (8.8)</td>
</tr>
<tr>
<td>$V_{c}$</td>
<td>28.3 (10.9)</td>
</tr>
<tr>
<td>$T_{si}/T_{tot}$</td>
<td>28.7 (16.7)</td>
</tr>
<tr>
<td>$V_{c}/V_{ti}$</td>
<td>11.8 (2.7)</td>
</tr>
<tr>
<td>MCA/V_{ti}</td>
<td>2.0 (3.0)</td>
</tr>
</tbody>
</table>

Values are means (SD) expressed as percent. The data were derived from individual coefficients of variation (CV%) for each parameter in each of the five asthmatic patients during the second bronchial challenge with methacholine in Experiment 2. Data are given after saline inhalation, and after the threshold provocative dose, i.e. when FEV₁ had declined at least 20%. See Table 1 for a definition of abbreviations. Statistical comparisons using the Student's $t$-test on log transformed data between parameters from the 1.5- and the 15-min interval, after saline inhalation and after the threshold dose. *$P<0.05$; †$P<0.01$.

non-linear model did not affect the calculation of the ventilatory pattern variability.

EXPERIMENT 3

The breath-to-breath intra-individual variability for the breathing pattern parameters is presented in Table 4. The variability of $V_{ti}$ and $V_{c}$ was significantly lower when breathing through a mouthpiece and a PTM than during natural breathing over 5 min ($P<0.05$; Table 4).

Discussion

In order to assess the significance of changes in ventilatory pattern in asthmatics, it is essential to know the breathing pattern variability at rest and during obstruction. In this study, the baseline breath-to-breath variability of the breathing pattern parameters was considerable, while on a day-to-day basis variability was less. Indices of ventilatory drive and tidal volumes were more variable than those of rib cage and abdominal phasing, respiratory timing and rib cage contribution to tidal volume. Variability did not change after histamine- or methacholine-induced bronchoconstriction (FEV₁ fall>20%) compared to after saline inhalation. There were considerable differences in variability between the various ventilatory pattern components. Therefore, in order to interpret the significance of changes in a ventilatory pattern component, its specific variability must be taken into consideration. A detailed discussion of the changes in the mean values of the breathing pattern components during the repeated

Table 4  Breath-to-breath intra-individual variability (CV%) in breathing pattern parameters during respiratory inductive plethysmography (RIP) recorded breathing and during breathing through a mouthpiece connected to a pneumotachograph (PTM) and wearing a noseclip in seven asthmatic patients

<table>
<thead>
<tr>
<th></th>
<th>RIP recorded breathing</th>
<th>Breathing through a PTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_R$</td>
<td>18.6 (15.3)</td>
<td>12.4 (6.6)</td>
</tr>
<tr>
<td>$V_{ti}$</td>
<td>25.5 (14.8)</td>
<td>14.1 (4.9)*</td>
</tr>
<tr>
<td>$V_{c}$</td>
<td>21.6 (10.8)</td>
<td>14.6 (5.1)*</td>
</tr>
<tr>
<td>$T_{si}/T_{tot}$</td>
<td>12.6 (3.9)</td>
<td>12.6 (4.1)</td>
</tr>
<tr>
<td>$V_{c}/V_{ti}$</td>
<td>19.4 (7.0)</td>
<td>16.6 (4.5)</td>
</tr>
<tr>
<td>MCA/V_{ti}</td>
<td>9.5 (8.9)</td>
<td>10.5 (9.1)</td>
</tr>
</tbody>
</table>

Values are means (SD) expressed as percent. The data were derived from individual coefficients of variation (CV%) for each parameter in each of the seven asthmatic patients at baseline in Experiment 3. See Table 1 for a definition of abbreviations. Statistical comparisons using the Student's $t$-test on log transformed data between parameters during RIP recorded breathing and those during breathing through a PTM. *$P<0.05$.

HiCh and MeCh undertaken in this study is given elsewhere (22).

The present study used RIP for indirect accurate monitoring of the spontaneous pattern of breathing (1, 19-21). The use of a mouthpiece or a mask connected to a PTM or to a spirometer during breathing pattern analysis is controversial since such equipment can induce changes in ventilation. Switching the route of breathing from, in most cases,
predominantly nasal to obligatory oral breathing changes airflow resistance, the volume of the external and the internal dead space and causes trigeminal nerve stimulation: \( V_t \) and \( V_{15} / T_{15} \) increase and ventilation is changed variably (15-18). Furthermore, it can mask the true changes in the ventilatory pattern during challenge (1,9). A lower variability for \( V_n \) and \( V_{15} \) were found when breathing through a mouthpiece and a PTM, as compared to natural breathing, indicating the need of using indirect methods for assessing the natural breathing pattern. The effect on variability from using a short time interval (1.5 min) for ventilatory pattern analysis in this study as compared to the 15-min interval used by Tobin et al. (14) was assessed in Experiment 2 during MeCh. The orders of the variability of the different parameters were similar irrespective of using a 1.5-min or a 15-min time interval. The variability was greater during the 15-min interval, probably due to cyclic variations in respiration which occur with different frequencies (37). Lenfant et al. distinguished a fast oscillation with a period of 2-6 breaths, a slow oscillation lasting 25-50 breaths, and an even slower oscillation over 150-200 breaths. When using a shorter period for breathing pattern analysis, the effect of the slower oscillations is filtered out and the variability may, therefore, be less.

Previous studies using either a PTM or a spirometer have demonstrated a negative correlation between \( V_t \) and \( f_R \). It has been suggested that although recurring changes are found in \( V_t \) and \( f_R \), their product \( (V'_{15}) \) remains relatively constant (38). Furthermore, findings of a positive correlation between \( V_n \) and \( T_n \) have led to the conclusion that \( V_n / T_n \) is held constant from breath-to-breath despite variations in \( V_t \) and \( T_t \) (39). However, neither \( V_n / T_n \) nor \( V'_{15} \) were measured directly in any of these studies (38–39). In contrast, the present authors and Tobin et al. (14) have obtained breath-to-breath measurements of \( V_n / T_n \) and \( V'_{15} \), and found a greater variability in \( V_n / T_n \), and \( V'_{15} \) than in \( f_R \). Tobin et al. (14) found that indices of ventilatory drive and tidal volume were more variable than indices of respiratory timing. The present results, obtained after saline and after histamine- or methacholine-induced bronchial obstruction in asthmatics, are similar to those presented by Tobin et al. in healthy semi-recumbent subjects (14). However, the breath-to-breath variability for MCA/\( V_{15} \) (mean CV 1.3%) and for \( V_n / V_{15} \) (8.7%) in the present study are much lower than those previously reported (11,1 and 22.6%, respectively) (14). This may partly be explained by different postures. This study used the sitting position (mean \( V_n / V_{15} \) of 67%), while Tobin et al. used the semi-recumbent position (mean \( V_n / V_{15} \) of 42%). Despite that, it seems that the subjects in the present study displayed a more regular rib cage to abdomen contribution and phasing between the compartments. Furthermore, the day-to-day variability of \( V_n / V_{15} \) (12.1%) in this study was much lower than in Tobin et al.'s study (28.4%).

Asthmatics generally demonstrate a different pattern of breathing than normal subjects do: \( V_{15} / V'_{15} \) and \( V_n / T_n \) are elevated, and \( T/T_{15} \) is lowered (10,11). The baseline values for \( V_n / T_n \), \( V'_{15} \), and \( V_{15} / T_{15} \) in this study were greater than those previously reported in asymptomatic asthmatics (10), but less than those in symptomatic asthmatics (11). The present data of \( V_{15} / T_{15} \), and \( V_{15} / T_{15} \) are elevated, and \( T/T_{15} \) is lowered (10,11). The baseline values for \( V_{15} / T_{15} \), \( V'_{15} \), and \( V_{15} / T_{15} \) in this study were greater than those previously reported in asymptomatic asthmatics (10), but less than those in symptomatic asthmatics (11). The present data of \( V_n / T_n \) and \( V_n / T_n \) are higher than those in the variability study of Tobin et al. in healthy subjects (14), indicating a heightened baseline respiratory drive in the present patients.

To the author's knowledge, only one study of the breathing pattern variability in asthmatics has been published previously using an indirect method for ventilatory monitoring (24). Kuratomi et al. used transthoracic impedance, calibrated for ventilatory volume, to assess \( V_n \) variability in restrictive and obstructive patients (24). They found a low \( V_n \) variability (mean CV 18%) in the restrictive patients and a high variability in asthmatics during a spontaneous asthma attack (36%) which decreased after relief of obstruction (22%). In contrast, Daubenspeck found that external resistive loading in normal subjects reduced the variability of \( f_R \) and \( V_{15} / T_{15} \). His finding is in line with the minimal work rate of breathing theory for ventilatory control (23). With resistive loading, deviations from the optimal respiratory frequency (i.e. that giving the lowest work of breathing) heightens the work of breathing more than during non-loaded breathing, thereby decreasing the variability in respiratory frequency. The same discussion can be applied to \( V_n \) deviations during elastic loading.

The present study found no significant changes in variability when bronchial obstruction had been induced by histamine or methacholine. The discrepancy between these findings and those of Kuratomi et al. (24) might depend on the influence of anxiety during a spontaneous asthma attack as compared to the more controlled situation during a bronchial challenge performed in an experienced subject.

The different respiratory responses to internal vs. external resistive loading, as found by Kelsen et al. (40), may explain the differing results in the study by Daubenspeck (23) and those in the present study. The physiological mechanism for the lack of decrease in variability as seen during external resistive loading
increases the variability which, however, from a minimization of the work of breathing point of view is expected to decrease. Mador et al. found that changes in mental activity influence ventilatory pattern variability: noxious stimulation (staring at a bright light) increased the variability of all breathing pattern parameters, and audiovisual stimulation (watching television) increased $V_n$ variability (41). The decreased $V_n$ variability during relief of a spontaneous asthma attack as found by Kuratomi et al. might therefore be explained by anxiety effects (24). The breathing pattern variability in the present study did not change after induced bronchial obstruction. Therefore, no evidence of altered mental activity associated with anxiety was found.

Ventilation may be expressed as the product of ventilatory drive and ventilatory timing as: $V' = (V_n/T_l)(T_l/T_{TOT})$ (5). Since the variability of both $V_n$ and $V_n/T_l$ was greater than that of $T_l/T_{TOT}$, the findings in the present study indicate that ventilatory timing is held more constant by the respiratory control system than ventilatory drive and ventilation, which is in accordance with the study by Tobin et al. (14).

In conclusion, in asthmatics the ventilatory pattern is quite reproducible at rest and during bronchial challenge on a day-to-day basis, despite considerable breath-to-breath variability. Ventilatory drive and tidal volumes are more variable than the rib cage and abdominal phasing, the respiratory timing and the rib cage fraction of tidal volume. The lack of difference in variability between rest and mild to moderate induced bronchial obstruction indicates that anxiety or minimization of the work of breathing mechanism are not important for the control of respiration in this situation.

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References


