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CO_2 response and pattern of breathing in patients with symptomatic hyperventilation, compared to asthmatic and normal subjects

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ABSTRACT: We studied six patients with symptomatic hyperventilation, using new techniques to quantify baseline variability of respiratory variables, and to assess CO_2 sensitivity around the control point using a stimulus not detectable by the subject. We compared them with six normal subjects and six patients with mild asthma. Symptomatic hyperventilators had normal mean ventilation and end-tidal carbon dioxide tension (P_{ETCO_2}) at rest. Asthmatic subjects had higher ventilation and lower P_{ETCO_2}. Symptomatic hyperventilators had a larger number of sighs and abnormally wide fluctuations in baseline for inspiratory time, expiratory time, and P_{ETCO_2}. These could not be explained by an abnormal ventilatory response to a transient CO_2 input; the transient response near the control point was undoubtedly normal.

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The so-called hyperventilation syndrome has received considerable attention recently. It refers to patients who complain of a variety of unrelated somatic symptoms (*e.g.* paraesthesiae, chest pain, palpitations) which appear to be associated with spontaneous overbreathing and may be reproduced by voluntary hyperventilation. Some of these patients have chronic hypocapnia, and some do not. The definition of the syndrome has not been agreed [1]. Because our subjects did not have chronic hypocapnia, but did have symptoms reproduced by hyperventilation, we prefer to describe them as having symptomatic hyperventilation (SHV) rather than the hyperventilation syndrome. It is not clear what aspects of respiratory control are abnormal, and why, in such patients. It is this aspect which we have examined.

Breathing in patients with SHV tends to be irregular. We introduce here a new technique to quantify the baseline variation in any respiratory variable, allowing for the statistical non-stationarity of the signal [2]. Such patients may find respiratory stimuli unpleasant. We have developed a new method for testing CO_2 response using stimuli so small that they are undetectable to the subjects [3]. The combination of these techniques allows us to consider whether any demonstrated irregularity of breathing can be explained by abnormal sensitivity to CO_2 around the control point.

We compared our patients to normal and mildly asthmatic subjects.

Methods

Subjects

We studied six patients with SHV. All complained of typical symptoms which could be reproduced by voluntary hyperventilation. The most common symptoms were related to breathing: five felt unable to breathe deeply, and a sixth complained of feelings of suffocation; two had air hunger, and three noticed rapid breathing; four complained of chest pain; five had palpitations.

Underlying organic disease was excluded as far as possible. All had normal spirometry, lung volumes and transfer factor for carbon monoxide. Morning and evening records of peak expiratory flow rate showed no abnormal variability, thus excluding as far as possible asymptomatic asthma. Chest X-ray films, ECGs and routine blood screens were normal. There was no past history of serious respiratory disease.

We compared this group with six normal subjects, and with six asymptomatic patients with asthma controlled by bronchodilator therapy alone. Groups were reasonably matched for age and sex (table 1).

Protocols

Subjects attended the laboratory at 10 am on the

morning of any study having eaten a light early breakfast at least 2 h previously. They had been asked not to take coffee, tea, alcohol or hypnotic drugs for the 12 h prior to the study. All subjects had attended the laboratory on a previous occasion to familiarize themselves with the equipment. Throughout each experiment the subjects sat in a comfortable chair listening to soft music through ear-phones in a laboratory heated to between 20 and 22°C.

Table 1. – Age, sex and basic lung function for the three groups

	Hyperventilator	Asthmatic	Normal
Age yrs (mean and range)	29 (23–41)	27 (21–39)	30 (24–37)
Sex	4F, 2M	4F, 2M	3F, 3M
Mean PEFR $l \cdot min^{-1}$ (±SD)	526 (89)	450 (33)	530 (69)
Mean FEV_1/FVC % (±SD)	73 (8)	68 (15)	83 (7)

PEFR: peak expiratory flow rate; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

1) *Measurement of resting breathing pattern.* On arrival in the laboratory subjects rested quietly in a chair for 20 min before applying the mouthpiece of the breathing circuit. Data from the first 5 min of each run was discarded. Recording continued for 25 min, sufficient to record at least 300 breaths.

2) *Ventilatory response to carbon dioxide.* After a 10-min rest period subjects again breathed through the mouthpiece. After 5 min, pure CO_2 was injected at a low flow rate into the inspiratory circuit through a 1.2 *l* fan-stirred mixing chamber close to the mouth. The flow of CO_2 was controlled at 0.4 $l \cdot min^{-1}$ ambient temperature and pressure dried (ATPD) by a rotameter (Fischer Controls Ltd), and the CO_2 stimulus was delivered for one minute. Maximum inspired carbon dioxide tension (P_{ICO_2}) with this method is about 35 mmHg. Recordings were continued for 5 min following this stimulus. Each experiment was repeated three times in each subject in the same session. No subject detected the stimulus or the increase in ventilation produced by the stimulus.

Measurements

Subjects breathed air from an open respiratory circuit, through a Rudolph No. 2700 valve to separate inspiratory and expiratory gas flows. Inspiratory and expiratory flow was measured with Fleisch No.4 pneumotachographs and Validyne MP45 differential pressure transducers calibrated at the start of the experiment with a 3 *l* syringe. CO_2 profiles were measured at the mouthpiece by a Centronic MGA 200 mass spectrometer, calibrated with three gas mixtures of known concentration at the start and end of the experiment. All signals, together with an event marker to time the start of CO_2 inhalation, were recorded on magnetic tape on a Racal FM tape recorder, and transcribed onto a six channel Gould 2600 S pen recorder. Tape signals were subsequently played back and analysed on a PDP 11/23 computer, sampling at 100 Hz to derive values for tidal volume (VT), inspiratory and expiratory times (TI and TE), breathing frequency (f) and end-tidal carbon dioxide tension (P_{ETCO_2}) [4].

Analysis

1) *Resting breathing pattern.* We wished to dissect from the signal the underlying baseline variation (non-stationarity). The method is more fully described elsewhere [2], but essentially consists of the following steps.

For any given variable (*e.g.* VT, P_{ETCO_2}) we have a series of results from at least 300 breaths. Then:

a) remove all breaths with values differing from the mean by greater than 2.5 SD (sighs) and replace them by the mean of values from the preceding and following breaths;

b) remove random high frequency noise, using a Butterworth filter with corner frequency adjusted repeatedly to remove maximum noise (*i.e.* no significant non-random structure is deleted);

c) the remaining signal is the true baseline variation;

d) define the turning points in the signal and by least squares regression fit the linear segments.

Thus the signal is finally characterized as a series of segments with lengths (in numbers of breaths) and excursions (in units depending on the variable chosen) which objectively define the baseline variability (fig. 1). Larger excursions in general denote poorer control. Differences between groups for mean values of segment length and excursions were assessed by Student's t-test.

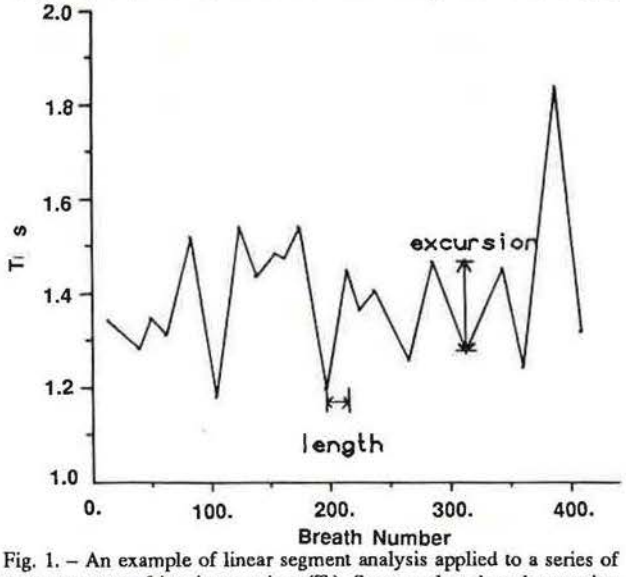

Fig. 1. – An example of linear segment analysis applied to a series of measurements of inspiratory time (TI). Segment length and excursion are assessed as illustrated.

2) *Ventilatory response to CO_2.* Breath by breath values for the derived variables were located in time at the central point of the relevant breath (TI+TE)/2, and time aligned

using the event marker for onset of CO_2 breathing as the reference point. The ensemble average for all variables was then obtained using 15 s bins. Ensemble averaging was performed for each subject (average of three responses) and for each group (average of eighteen responses).

Results

1) Resting breathing pattern

Mean group values (for at least 300 breaths from each subject) were calculated for relevant variables and tested for group differences by Student's t-test. Asthmatics showed a significantly higher frequency (15.5 breaths·min^{-1}) and ventilation (11.1 *l*·min^{-1}) and lower P_{ETCO_2} (37 mmHg, 4.9 kPa) than both normal (13.9, 9.7, 40, 5.3) and SHV (13.0, 8.1, 41, 5.5) groups. There were no other significant differences.

Maximum and minimum values. We obtained these for each variable in each individual and averaged the results for each group (table 2). In general, the SHV patients had the widest range, with asthmatics intermediate between SHV and normal subjects. This applies to all variables except V_T and is most clearly seen for respiratory rate.

Baseline movement. We took mean values for segment length (fig. 1) and found no significant differences between the groups. For segment excursion (table 3) there are significant differences between control and SHV for T_I, T_E and P_{ETCO_2}, implying greater baseline movement and poorer control.

Sighs. Defined as breaths with a tidal volume greater than 2.5 SD above the mean for the run, these occurred most frequently in SHV subjects (mean values 8 per run, range 4–18). Sighs occurred with similar frequency in controls, (mean 4, range 1–9) and asthmatics (mean 3, range 1–10).

2) Ventilatory response to CO_2

Group means were taken for control values of P_{ETCO_2} and $\dot{V}$, (mean for one min pre-stimulus), peak P_{ETCO_2} and $\dot{V}$ and by subtraction ΔP_{ETCO_2} and $\Delta\dot{V}$ (table 4), and tested for differences between groups (figs 2 and 3).

We also calculated an index of CO_2 response gain ($\Delta\dot{V}$ /ΔP_{ETCO_2}), and tested for differences between groups using the logarithm of the ratio.

In short, there was no significant difference in response to a transient CO_2 stimulus between groups. Asthmatics, as found above, had a higher control ventilation and lower P_{ETCO_2} than both control and SHV groups, which were indistinguishable.

Table 2. – Mean maximum and minimum values with differences, for the three groups, (±SD)

		T_I s	T_E s	f b·min^{-1}	V_T *l*	$\dot{V}$ *l*·min^{-1}	P_{ETCO_2} mmHg (kPa)
Control	min	1.5±0.3	1.7±0.3	9.0±2.2	0.5±0.1	5.8±1.3	37.4±2.1 (5.0±0.3)
C	max	3.0±0.9	4.7±1.2	18.7±9.7	1.8±0.7	17.8±0.7	43.5±1.3 (5.8±0.2)
Asthma	min	0.9±0.2	1.6±0.4	8.5±2.2	0.4±0.1	4.8±0.9	34.0±3.3 (4.5±0.4)
A	max	2.9±0.8	5.8±1.5	22.0±4.9	1.5±0.9	18.2±7.1	40.1±4.8 (5.3±0.6)
Hyperventilation	min	0.8±0.4	1.1±0.5	6.6±1.8	0.4±0.5	2.6±0.9	35.1±4.6 (4.7±0.6)
H	max	3.8±1.4	6.2±1.3	30.5±10.6	1.8±0.7	17.6±0.3	44.2±2.6 (5.9±0.3)
	C	1.53	2.92	9.73	1.36	12.04	6.10 (0.8)
Difference	A	2.06	4.13	13.55	1.12	13.42	6.14 (0.8)
	H	3.01	5.10	23.90	1.40	14.97	9.10 (1.2)

Each subject generates a single maximum and minimum value for respiratory variables in a single run, *i.e.* n=6 for each listed mean.T_I: inspiratory time; T_E: expiratory time; f: breathing rate; V_T: tidal volume; $\dot{V}$: minute ventilation; P_{ETCO_2}: end-tidal carbon dioxide tension.

Table 3. – Mean values (±1SD) for segment excursion (fig. 1) in the three groups

		T_I s	T_E s	V_T l	$\dot{V}$ l·min^{-1}	P_{ETCO_2} mmHg (kPa)
Control	C	0.18±0.14	0.29±0.22	0.07±0.06	0.98±0.88	0.76±0.62 (0.10±0.08)
Asthma	A	0.14±0.13	0.29±0.27	0.07±0.07	1.07±0.78	0.72±0.08 (0.10±0.01)
Hyperventilation	H	0.24±0.21*	0.44±0.38*	0.09±0.07	1.25±0.08	1.19±1.31* (0.16±0.17)

*: signifies $p<0.05$ for H *vs* C. T_I: inspiratory time; T_E: expiratory time; V_T: tidal volume; $\dot{V}$: ventilation ; P_{ETCO_2}: end-tidal carbon dioxide tension.

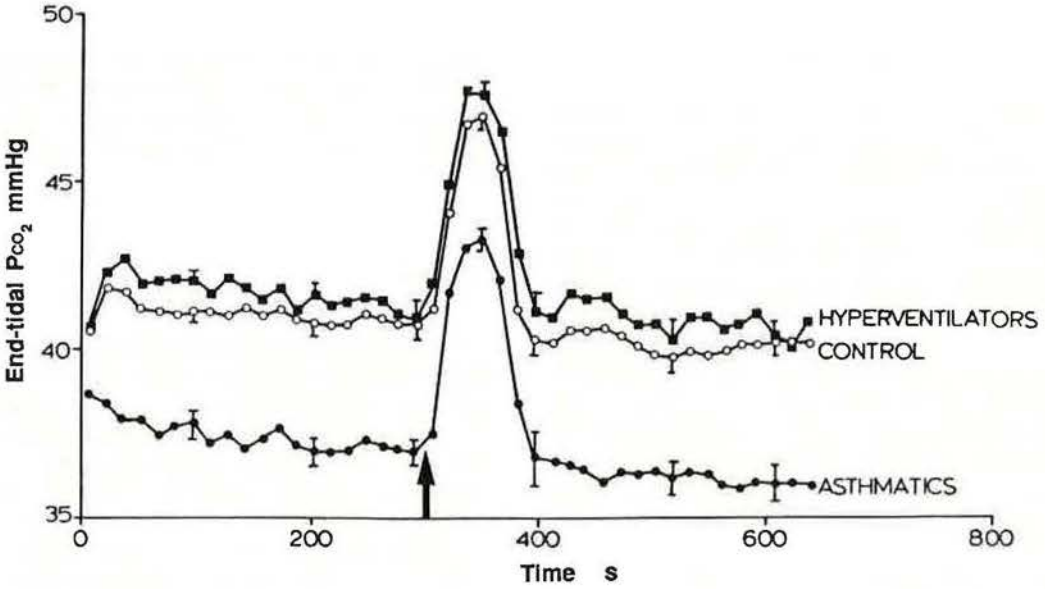

Fig. 2. – Mean transient response in end-tidal carbon dioxide tension (P_{ETCO_2}) in the symptomatic hyperventilators (SHV), asthmatic and control groups. CO_2 inflow starts at the arrow.

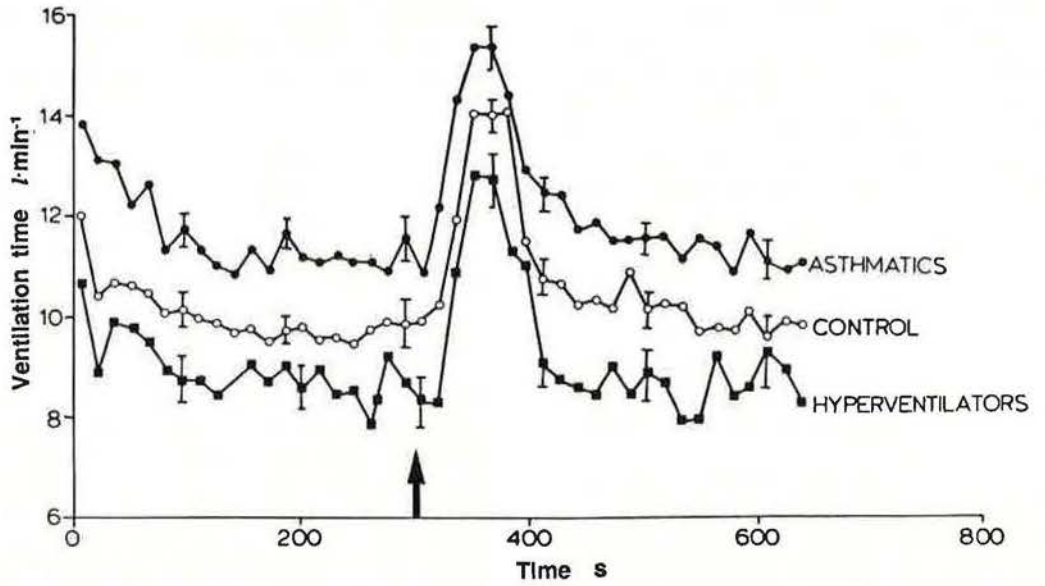

Fig. 3. – Mean transient response in ventilation ($\dot{V}$) in the symptomatic hyperventilators (SHV), asthmatic and control groups. CO_2 inflow starts at the arrow.

Table 4. – Peak changes in $\dot{V}$ and P_{ETCO_2} and their ratio, in the transient CO_2 response test

	Control P_{ETCO_2} mmHg (kPa)	ΔP_{ETCO_2} mmHg (kPa)	Control $\dot{V}$ $l \cdot min^{-1}$	$\Delta\dot{V}$ $l \cdot min^{-1}$	$\Delta\dot{V}/\Delta PETCO_2$ $l \cdot min^{-1} \cdot mmHg^{-1}$ ($l \cdot min^{-1} \cdot kPa^{-1}$)
Control	40.9±1.9 (5.5±0.3)	6.6±0.7 (0.9±0.1)	9.8±1.7	4.7±1.9	0.72±0.30 (5.4±2.3)
Asthma	37.2±3.6 (5.0±0.5)	6.6±1.6 (0.9±0.2)	11.5±1.8	5.0±1.5	0.77±0.27 (5.8±2.0)
Hyperventilation	42.4±3.4 (5.7±0.5)	7.1±1.2 (0.9±0.2)	8.6±1.5	4.5±0.6	0.65±0.17 (4.9±1.3)

There are no significant differences between groups. Figures are mean (±1SD). $\dot{V}$: minute ventilation; P_{ETCO_2}: end-tidal carbon dioxide tension; $\Delta\dot{V}$, ΔP_{ETCO_2}: peak changes in $\dot{V}$ and P_{ETCO_2} respectively.

Discussion

Typical symptoms of the hyperventilation syndrome outlined previously have been attributed to hypocapnia caused by overbreathing, and possible mechanisms have been suggested [5–7]. BASS and GARDNER [8] suggest that chronic prolonged intermittent hypocapnia must be demonstrated before chronic hyperventilation syndrome can be diagnosed, and that symptomatology alone is insufficient justification for the diagnosis. Other authors feel that typical symptomatology, particularly if more than one symptom is present and they are reproduced by hyperventilation provocation tests, is sufficient justification for the diagnosis [9–11]. A proportion of the patients fulfilling the above criteria (up to 30% of the series of patients studied by LUM [10]), have not shown measurable baseline hypocapnia under normal laboratory conditions.

We have no wish to enter the semantic dispute of what does or does not constitute the "hyperventilation syndrome". We describe here a defined group of patients with symptoms promoted by hyperventilation, abnormal breathing pattern at rest, and no hypocapnia.

Resting breathing pattern is known to be affected by the addition of a mouthpiece, noseclip and deadspace. Notably, with the addition of a mouthpiece (Mp) and noseclip (Nc) respiratory frequency tends to fall, and tidal volume to rise [12–14], thus possibly slowing the typical hyperventilator's rapid, shallow thoracic breathing [11]. TOBIN *et al.* [15] have demonstrated that patients with chronic anxiety state tend to have more regular breathing with a mouthpiece occluded by a noseclip. Despite this predicted alteration of breathing pattern with Mp and Nc our group of SHV patients still had breathing patterns which were demonstrably more irregular both in maximum and minimum respiratory indices achieved for the measured respiratory variables, and for baseline irregularity.

It is known that a single deep breath is capable of reducing P_{ETCO_2} by up to 15 mmHg and that most of the reduction in CO_2 during overbreathing is accomplished during the first 30 s. Thus hypocapnic alkalosis can be achieved very rapidly. Symptoms may be produced by changing arterial P_{CO_2} and not necessarily by permanently low P_{CO_2}. Our group of patients with symptoms typical of "hyperventilation syndrome" would support the notion that symptoms can be produced by transient changes in CO_2.

Asthmatics

The asthmatic group of patients had a significantly higher baseline respiratory frequency and tidal volume, and concomitantly lower P_{ETCO_2} than either control or SHV groups. Inducing moderate bronchoconstriction in normals causes similar increases in f and $\dot{V}$ [16] when breathing with Mp and Nc, whereas less invasive methods of measurement and similar degrees of bronchoconstriction do not cause these changes in f and $\dot{V}$ [17]. Mp and Nc breathing is known to decrease inspiratory resistance [14] by decreasing internal resistive load, and this has been suggested as a mechanism contributing to the decrease in f and increase in V_T seen in normals. Airway obstruction appears to increase ventilatory drive without chemical stimuli [5], possibly by increased vagal afferent input, although precise mechanisms are unclear. Thus Mp breathing may not alter breathing in asthmatics who already have increased internal resistive loads as much as in normals.

Our results in asthmatics agree with those of TAMURA [18], who also used Mp breathing, but not with TOBIN [15] who used external inductive plethysmography and found that the breathing pattern of asymptomatic asthmatics was no different from normals. Clearly use of Mp and Nc techniques alters the breathing pattern variably in different disease states, making comparisons with non-invasive studies difficult. The degree of variability of breathing pattern in our group of asthmatics was no different from normals, and despite having lower P_{ETCO_2} than both control and SHV groups asthmatics did not complain of symptoms typical of the "hyperventilation syndrome", adding further support to the notion that changes in CO_2 are more important than long-term CO_2 levels.

CO_2 responses

We opted to use an undetectable one-minute pulse of CO_2 as our stimulus, rather than steady-state or rebreathing methods as in both of these techniques the stimulus or change in respiration produced are detectable by the patient. An undetectable stimulus is an advantage in testing patients who complain of uncomfortable sensations associated with increased breathing.

Ventilatory response to the same delivered pulse of CO_2 was not significantly different between asthmatics, normals or SHV patients. The results in asthmatics agree with those of other investigators who have found that bronchoconstriction does not affect the chemoreceptor response [18, 19]. FOLGERING and COLLA [5] in a study of 51 patients with "hyperventilation syndrome" found that 19 patients either decreased ventilation or showed no change when exposed to CO_2 stimuli. They attributed this to a positive feedback mechanism operating, but it is difficult to be certain of this except in demonstrated steady-state conditions. Using a transient stimulus we found no such patients.

GARDNER *et al.* [20] found that patients with hypocapnia were operating below the CO_2 threshold, but patients such as ours with higher P_{CO_2} behaved normally to a steady-state CO_2 stimulus.

We have shown that the breathing pattern of patients with SHV is abnormal, not just in terms of abnormally large breaths or sighs or in terms of the range between maximum and minimum values (which reflects mainly the presence of sighs), but overall. While this difference might apparently be shown by taking mean values and standard deviations over a long run of breathing this is not strictly a valid approach, since the signal is demonstrably non-stationary, *i.e.* the mean is varying within the series of values considered (fig. 1, table 3). In our analysis, the sighs are considered separately and removed from the main analysis (see Methods).

These non-random, abnormally large fluctuations might have been caused by abnormal CO_2 chemoreceptor response. Our CO_2 response technique, designed to operate indetectably and test responses close to the control point, shows conclusively that this hypothesis is false. It seems perfectly possible that some non-reflex stimulus, such as anxiety, is over-riding the normal feed-back mechanisms and interfering with the precise control of normal breathing in these patients.

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RÉSUMÉ: Six patients atteints d'hyperventilation symptomatique ont été étudiés au moyen de nouvelles techniques pour quantifier la variabilité basale des variables respiratoires, et pour déterminer la sensibilité au CO_2 autour du point contrôle, au moyen d'un stimulus non détectable par la sujet. Nous les avons comparé à six sujets normaux et à six patients atteints d'asthme léger. Les sujets atteints d'hyperventilation symptomatique avaient une ventilation moyenne normale et une P_{ETCO_2} normale au repos à la fin d'une ventilation à volume courant. Les sujets asthmatiques avaient une ventilation plus élevée et une P_{ETCO_2} plus basse à la fin du volume courant. Les sujets atteints d'hyperventilation symptomatique avaient un plus grand nombre de soupirs et des fluctuations anormalement larges de la ligne basale pour les périodes inspiratoires, les périodes expiratoires, et pour la pression de CO_2 à la fin du volume courant. Ces anomalies ne peuvent trouver leur explication dans une réponse ventilatoire anormale à une stimulation transitoire par le CO_2, la réponse transitoire autour du point contrôle étant indubitablement normale.