Normalizing CO_2 in chronic hyperventilation by means of a novel breathing mask: a pilot study

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Abstract

Introduction: Chronic idiopathic hyperventilation (CIH) is a form of dysfunctional breathing that has proven hard to treat effectively.

Objectives: To perform a preliminary test of the hypothesis that by periodically inducing normocapnia over several weeks, it would be possible to raise the normal resting level of CO_2 and achieve a reduction of symptoms.

Methods: Six CIH patients were treated 2 h a day for 4 weeks with a novel breathing mask. The mask was used to induce normocapnia in these chronically hypocapnic patients. Capillary blood gases and acid/base parameters [capillary CO_2 tension (P_{capCO2}), pH, and standard base excess (SBE)] were measured at baseline and once each week at least 3 h after mask use, as well as spirometric values, breath-holding tolerance and hyperventilation symptoms as per the Nijmegen Questionnaire (NQ).

Results: The mask treatment resulted in a significant increase of resting P_{capCO2} (+0.45 kPa, $P = 0.028$), a moderate increase in SBE (+1.4 mEq/L, $P = 0.035$) and a small reduction in daily symptoms (−3.8 NQ units, $P = 0.046$). The effect was most pronounced in the first 2 weeks of treatment.

Conclusion: By inducing normocapnia with the breathing mask 2 h a day for 4 weeks, the normal resting CO_2 and acid/base levels in chronically hyperventilating patients were partially corrected, and symptoms were reduced.

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Authorship and contributorship
Troels Johansen: designed and performed study, analyzed data, cowrote article
Sandy Jack: contributed to design of study and analysis of data, cowrote article
Ronald Dahl: contributed to design of study and analysis of data, cowrote article

Ethics
The study was performed in accordance with the 2000 Declaration of Helsinki and was approved by the Ethics Committee of Central Jutland and the Danish Health and Medicines Authority. All patients gave their informed consent prior to their inclusion in the study.

Conflicts of interest
Sandy Jack declares to have no conflicts of interest. Ronald Dahl declares to have no conflicts of interest. Troels Johansen is a shareholder in, and the CEO of, Balancair ApS, the company that has applied for a patent on the mask technology. The work as CEO is unsalaried, and the company has no employees.

The study has been registered in the US National Library of Medicine registry (http://www.clinicaltrials.gov), with the identifier NCT01575665.

Introduction

Chronic idiopathic hyperventilation (CIH) is a condition of unknown etiology characterized by an alveolar ventilation (V_A) that is perpetually in excess of metabolic requirements, leading to a state of chronic hypocapnia, i.e. an arterial CO_2 partial pressure (P_{aCO2}) below 4.7 kPa (1) and in some cases as low as 2.7 kPa (2). This condition is associated with shortness of breath and exercise intolerance as well as chest pain/tightness, light-headedness, paresthesia and fatigue (2–4). In terms of exercise tolerance, activity level and general health status, CIH patients have been shown to be comparable with patients with severe chronic obstructive pulmonary disease (COPD) (5). An overlap with asthma has been seen in many cases (3, 6–9), although baseline spirometric values and lung volume parameters are often normal (2, 6). As such, CIH may be tentatively characterized as a functional disorder.

Concurrent chronic anxiety may be present (3, 4, 10), but this is far from always the case (3, 10, 11). Although panic disorder (PD) has in the past been hypothesized to be due to hyperventilation (12), more recent work strongly suggests that hyperventilation is secondary to panic attacks (or absent) and may possibly be triggered by a sudden *increase* in the CO_2 level (13, 14). A recent study showed a large treatment effect of both CO_2-lowering and CO_2-heightening breathing exercises in PD (15), an indication that the actual CO_2 level may be secondary in that disorder.

In general, hyperventilation and CIH clearly cannot be reduced to simply effects of anxiety or vice versa.

Compared with the marked respiratory alkalosis of acute hyperventilation attacks, the systemic pH value in CIH is only slightly above normal, whereas the bicarbonate level is much lower than in acute attacks, both effects being consequences of a renal compensation for the long-term hypocapnic state (3, 16). CIH is consequently characterized by a low P_{aCO2}, a large negative standard base excess (SBE) (signifying the renal compensation by excretion of bicarbonate that accompanies the respiratory alkalosis) and an arterial oxygen pressure above normal.

It has been hypothesized that these patients may have a lowered homeostatic *set point* for CO_2, their respiration being constantly elevated to maintain an abnormally low P_{aCO2}. This has been indicated by experiments showing that CIH patients seem to maintain a low CO_2 level both at rest, when exercising and in sleep (2, 17).

It is not fully known whether such an increase in ventilatory drive and/or decrease of the CO_2 set point are genetic or acquired traits, although a theory has been proposed that a period of hyperventilation (brought on by for example an extended period of anxiety or physical pain) can lower the CO_2 set point permanently, in effect making hyperventilation chronic (2, 18, 19).

In patients where CIH is present together with anxiety or asthma, a significant treatment effect has been gained from a normalization of the breathing pattern and systemic CO_2 level (7–10, 20, 21), as in the Buteyko breathing technique for asthma that has gained much interest during recent years, patient studies having shown a significant reduction of symptoms and inhalator use with this method (21).

In the above studies, the normalization of CO_2 partial pressure (P_{CO2}) was obtained through breathing exercises. These are in general demanding and time-consuming, and require either electronic biofeedback equipment or instruction and coaching from a proficient instructor. For this reason, it will be advantageous to design alternative treatment forms that can normalize CO_2 in a *user-passive* way. By such methods, it may be possible to treat the high proportion of patients who do not have the self-control and perseverance needed for regular and lengthy breathing exercises.

The present work examines the possibility of normalizing the CO_2 resting level and relieving symptoms by inducing normocapnia 2 h a day for 4 weeks using a novel breathing mask. The mask is user-passive in the sense that it raises the bodily CO_2 level without an active effort from the patient. The mask can therefore be used while performing other restful activities: reading, watching TV, etc.

On the basis of prior studies of long-term breathing of CO_2 rich air (22–24), we hypothesized that a gradual normalization of the acid-base status of the CIH patients might be possible, counteracting the renal pH compensation present (thereby re-establishing the 'CO_2 brake' on hyperventilation*) and perhaps raising the CO_2 set point (if this is indeed an entity) of these patients.

Materials and methods

With ethics committee approval and informed consent from all patients, we studied six patients with CIH, defined as a capillary CO_2 tension (P_{capCO2}) below

*In acute hyperventilation, the fall in systemic CO_2 produces an increase in systemic pH, thereby weakening the input from the chemoreceptors (hence the 'CO_2 brake'). When pH is normalized, this feedback mechanism is reduced (27).

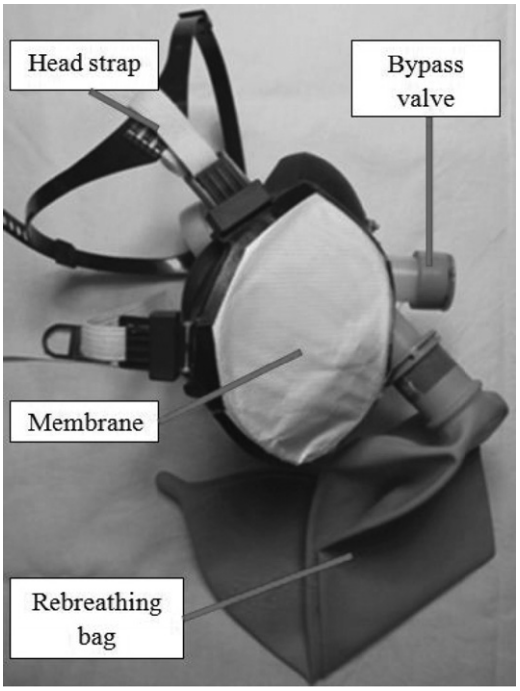

Figure 1. The partial rebreathing mask showing the membranes, rebreathing bag, head straps and bypass valve.

4.7 kPa and an SBE value more negative than −1.0, indicating a partially pH-compensated chronic hypocapnia.†

patients were excluded if their oxygen saturation level measured with a pulse oximeter (model: H100B, EDAN, Shenzhen, China) was below 95% at rest, which would signify that their increased ventilation and hypocapnia might be compensatory to an underlying pulmonary disease (in which case they would not be *hyperventilating*, defined as a ventilation in excess of metabolic requirements).

The intervention consisted of mask treatment for 2 h each day for 4 weeks in the patients' homes, with weekly examinations at the Department of Respiratory Diseases, performed at least 3 h after last mask use. At these examinations, the following data were measured: capillary blood gas values [P_{capCO2}, capillary O_2 partial pressure, pH and SBE, measured by an ABL90 blood gas analyzer (Radiometer, Copenhagen, Denmark)], venous electrolyte values (calcium, chloride, potassium, sodium, magnesium and phosphate, and total carbon dioxide), spirometric values [forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)], as well as a questionnaire used to quantify hyperventilation symptoms [the Nijmegen Questionnaire (NQ)]. Furthermore, a breath-holding test was performed, in which the patients held their breath after a normal exhalation to functional residual capacity, stopping when they felt the urge to breathe again, and this breath-hold tolerance (BHT) time was then recorded.

A profile view of the partial rebreathing mask is seen in Fig. 1, and a flow diagram is shown in Fig. 2.

The mask is a passive device, being independent of a supply of stored gas or electric power.

In use, it is fastened with the head straps so that the patient is wearing the mask. Part of the expired gas enters the rebreathing bag for subsequent rebreathing while the membranes and two-way bypass valve allow a flow of gas between the mask volume and the atmosphere. In this way, a steady state is established in which inspired CO_2 is raised and inspired oxygen is high enough to allow normal arterial oxygen saturation. The membranes are made from a porous and hydrophobic polytetrafluoroethylene material (i.e. a 'Goretex' type material) that is more diffusion-permeable to water and oxygen than CO_2, effectively making it possible to raise CO_2 with a lower decrease in inspired oxygen and a smaller increase in inspired water vapor compared with what can be achieved with a rebreathing mask without such membranes.

Technical tests with the masks prior to the patient study confirmed that a steady state in blood gas tensions is achieved when the mask is in use, raising

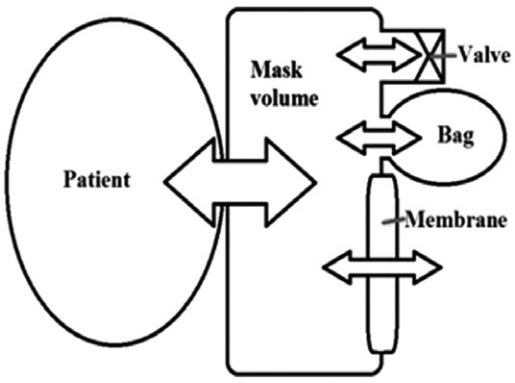

Figure 2. Flow diagram of the partial rebreathing mask. By adjusting the two-way bypass valve, the level of rebreathing can be varied.

†Capillary blood samples have been shown to be comparable with arterial blood regarding the values of P_{CO2} and pH (32), and compared with artery blood sampling, capillary blood sampling has the advantage of being less stressful and anxiety provoking to the patient, thereby minimizing the risk of inducing changes in ventilation by the act of taking the blood sample (or by the patient's anticipation of having an arterial sample taken).

Table 1. Literature reference values for healthy controls, together with baseline values, end-of-treatment values and computed changes for six patients with chronic idiopathic hyperventilation treated for 4 weeks, with a partial rebreathing mask 2 h per day

		Reference value	Reference	Baseline value	End-of-treatment value	Change (absolute)	*P* value, Wilcoxon signed-rank test*
P_{capCO2}	(kPa)	5.40 (0.44)	(31)	3.96 (0.30)	4.41 (0.39)	+0.45 (0.31)	0.028
pH		7.402 (0.016)	(31)	7.45 (0.03)	7.43 (0.03)	–0.02 (0.02)	0.075
SBE	(mEq/L)	0.48 (1.35)	(31)	–3.8 (1.3)	–2.3 (1.2)	+1.4 (1.0)	0.035
BHT	(s)	58 (23)	(2)	18 (5)	22 (7)	+4 (6)	0.172
Nijmegen score		12 (9)	(2)	23.8 (9.4)	20.1 (7.7)	–3.8 (3.1)	0.046

For two subjects, end of treatment was reached after 2 weeks, in one case because the patient had reached normal blood gas and acid base status, and in the other case because of events unrelated to the treatment protocol.

All data are mean values (standard deviation).

*Test of no difference between baseline and end of treatment.

P_{capCO2}, capillary CO_2 tension; SBE, standard base excess; BHT, breath-hold tolerance.

end-tidal CO_2 (P_{ETCO2}) by up to 25%, with only a 1%–2% drop in oxygen saturation measured with a pulse oximeter.

At the visits each week of the 4-week treatment period, the bypass valve was adjusted while the patient was wearing the mask, and their P_{ETCO2} level was being measured with a Capnocount Mini capnometer (Weinmann, Hamburg, Germany). The valve was adjusted so as to raise P_{ETCO2} to the normocapnic range [4.7–6.0 kPa (25)] and preferably as close to 5.3 kPa as possible. This was then the valve setting used during the following week of home mask treatment.

The parameter used in the sample size calculation‡ was the change in SBE during the treatment period, as a sign of normalization of acid/base status and CO_2 level. The aim of the study was to get a first *in vivo* test of the treatment concept and so did not include a control group.

The Stata software version 11 (StataCorp, College Station, TX, USA) was used to conduct paired Wilcoxon signed-rank tests comparing baseline values with end-of-treatment values. A P value of <0.05 was considered to be statistically significant, although bearing in mind that a possible placebo effect and regression toward the mean would need to be taken into account when interpreting the results.

Results

The patients were five women and one man between 23 and 57 years of age. The height, weight and body mass index of the group were within the normal range.

‡For a power of 0.9 at a significance level of $P < 0.05$, showing a minimal sample size of five patients. Calculated with the Stata 11 software package.

Table 1 shows normal reference ranges from the literature for selected parameters, baseline values for the patients at the beginning of the treatment period as well as the changes recorded at the end of the treatment period.

The patients had normal spirometric values {FEV_1% of predicted = 97.1% [standard deviation (SD) 17.5], FVC% of predicted = 106.7% of normal [SD 19.0], FEV_1/FVC = 78.0% [SD 6.2]}, and no significant changes in spirometry were seen over the course of the treatment period.

As can be seen in Table 1, the patients were markedly hypocapnic compared with healthy control reference values for P_{capCO2}, and the partial pH compensation present (i.e. a negative SBE) signified that this hyperventilation was a chronic or subacute condition.

According to the data from the NQ, the patients were on average slightly above the 23 points used as a signifier of the hyperventilation syndrome, although with a high variability among the patients. The BHT was markedly low compared with reference values for healthy persons (2, 26).

In the study, four of the six patients completed the 4 weeks of mask treatment. One patient was withdrawn from the study after 2 weeks because of having attained a normalization of P_{capCO2} and acid/base status in the course of the treatment (i.e. the patient's values of P_{capCO2}, SBE and pH were within the normal reference range at visit 3). One other patient (the only male patient) was withdrawn after 2 weeks because of circumstances unrelated to the study. No adverse events occurred during the treatment period.

Comparing before and after values from Table 1, a statistically and clinically significant increase in mean resting CO_2 level was seen, from 3.96 (SD 0.30) to 4.41 (SD 0.39) kPa (see Fig. 3), accompanied by a reduction

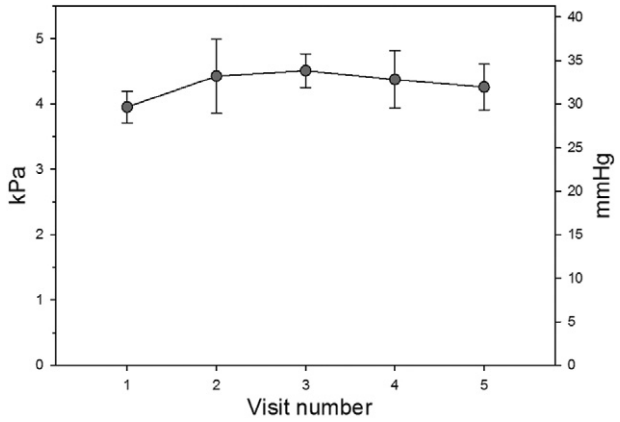

Figure 3. Capillary CO_2 partial pressure over the course of the 4 weeks of mask treatment showing mean values ± standard deviations.

in negative SBE from −3.8 (SD 1.3) to −2.3 (SD 1.2) mEq/L (see Fig. 4). Symptom severity as measured by the NQ displayed a fall over the treatment period (Fig. 5), although this effect only just reached significance ($P = 0.046$) and was of small clinical significance (a mean reduction of 16% in symptom score, ±13%).

A small increase in mean BHT over the course of the treatment period was seen, but this effect did not reach significance.

The improvements in acid/base status were largest during the first 2 weeks of the treatment (see Figs. 3 and 4), the gains subsequently being partially offset although the changes between start and end of treatment were still statistically significant. Concerning serum electrolytes, increases were seen in all ion concentrations except chloride, although only for calcium did this tendency reach significance.

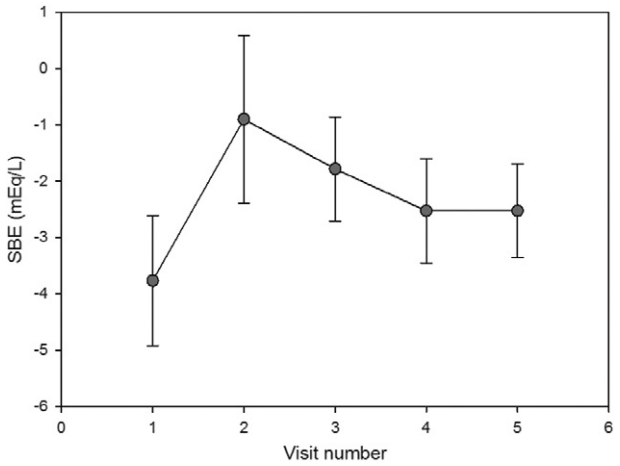

Figure 4. Capillary standard base excess (SBE) over the course of the 4 weeks of mask treatment, showing mean values ± standard deviations.

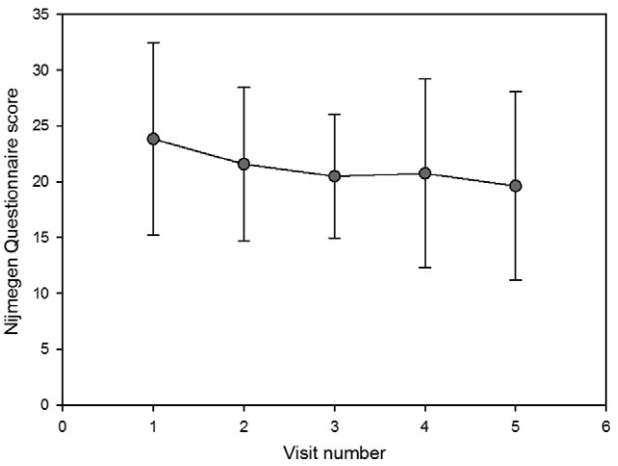

Figure 5. Nijmegen Questionnaire score over the course of the 4 weeks of mask treatment showing mean values ± standard deviations.

Using the Stata software package, a series of preliminary regression analyses were conducted using clustered data and robust standard errors in order to look for possible linear correlations between, on one side, blood gas values and, on the other, NQ score, BHT and mask parameters.§

In this analysis, an interesting correlation was shown between the value of SBE and the change in valve setting in the week prior to the visit at which the SBE was measured (see Fig. 6), showing that the *change* in valve setting had a statistically significant correlation with the SBE value but that the absolute valve setting itself did not show such a correlation with SBE.

Discussion

At baseline, the patients showed many of the traits of CIH that have been found in earlier studies: a low P_{aCO2} with a large negative base excess, pointing to a chronically raised ventilation, together with a high incidence of reported hyperventilation symptoms. The patients also displayed a markedly low breath-holding tolerance, a trait that is also well-known in CIH (2).

The hypothesis was tested that the mask treatment would lead to a normalization of blood gas and

§These analyses were performed as linear regressions using robust standard errors and clustered data from all visits (all visits of each patient constituting a cluster) – and bearing in mind that any result should be viewed with a critical eye because of the small sample size.

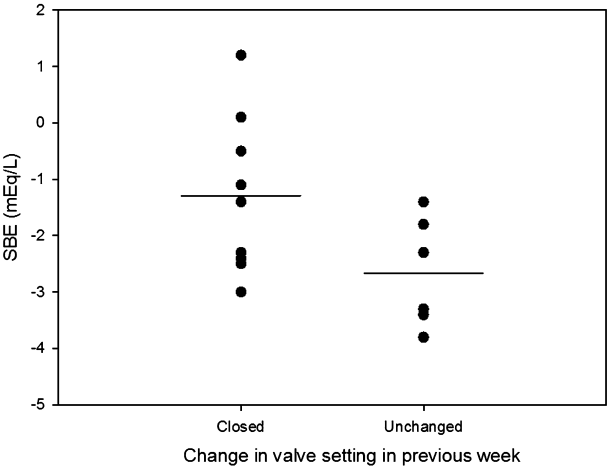

Figure 6. Data for patient visits 2–5 showing relationship between SBE and the change in setting of the mask bypass valve during the treatment week prior to the measurement: 'Closed' meaning the valve had been reset at a higher rebreathing level during the previous week (this included by definition all the second visits of the study) and 'Unchanged' meaning that the valve setting had been unchanged during the previous week. Figure shows individual data points (closed circles) and means (horizontal bars).

acid/base parameters. This was partially confirmed by the data, P_{capCO2} showing a mean increase of 11%, with negative SBE being reduced by a mean of 38% (see Table 1). At the time of measurement, the patients had not used the mask for at least 3 h so it seems likely that the change in P_{capCO2} reflects a change in ventilation and not a carry-over residual effect from the increase in CO_2 and bicarbonate level induced during the mask use. Because the minute ventilation was not recorded, this could however not be conclusively verified.

Also, it is a significant observation that the effect on blood gases was greatest at the beginning of the 4-week treatment period (see Figs. 3 and 4). Judging from the patient log book, there is no indication of a fall in compliance over the treatment period that could explain this effect. Rather, it may be that the ventilatory response of the CIH patients to the rebreathing gradually increased, compensating more fully for the higher level of inspired CO_2.

With the development of chronic hyperventilation, the pH compensation will partly offset the normal 'CO_2 brake' on hyperventilation (27), perhaps making hyperventilation self-sustaining also when the original stressor producing the hyperventilation has disappeared (2, 18, 19). The mask treatment reduced the metabolic pH compensation (signified by the decrease in negative SBE), but this did not by itself seem to lead to a 'virtuous circle' of reduced hyperventilation, rather this seemed to be dependent on the continual use of the mask.

The etiology of CIH remains elusive, but these preliminary data do indicate that the normal CO_2 resting point *can* be altered. Indeed, the results of the study contradict the presence of a fixed set point for CO_2, at least for this patient group.

Seeing that this pilot study led to a partial normalization of blood gas and acid-base values, the treatment concept warrants follow-up controlled studies, exploring for example the effect of prolonged mask treatment and/or a continual increase of rebreathing level over the treatment period. Another interesting possibility would be the option of coupling the mask directly with a capnograph so that the valve setting could be continually adjusted by the patient to induce a stable normocapnic state – in the study, the precise increase of P_{capCO2} when the patients were using the mask at home was not known.

Although hampered by a low sample size, the correlation analysis did yield the interesting observation that *no* significant correlation could be seen between the systemic CO_2 level (P_{capCO2} and bicarbonate concentration) and the symptom severity as measured by the NQ. Whereas the effect on P_{capCO2} was partially offset during the last half of the treatment period, the symptoms showed a steady (although slight) decline. This may be indicative of a secondary effect (placebo or otherwise) of the treatment, not directly correlated with the blood gas values or ventilation level.

Another correlation that was notably absent was between the systemic CO_2 level and the BHT. The technique used corresponds to the 'control pause' used in the Buteyko asthma technique, which by Buteyko practitioners is used as a measure of the level of hyperventilation of a person (26, 28). In the Buteyko technique, a low BHT is supposed to be correlated with the degree of hyperventilation. No such correlation was found (this being in accordance with another recent study of the Buteyko technique (26)), although the patients did have a BHT that was markedly lower than the normal value reported in the literature (2).

Previous studies have found altered levels of blood electrolytes in hyperventilation. Specifically, low levels of potassium and phosphate ion have been seen in hyperventilation patients (3, 4, 29), but no such pattern was seen in the data, although it was an interesting observation that all *positive* electrolytes increased during the treatment period perhaps as a compensatory response to the gradual increase in the *negative* bicarbonate ion.

Some of the research into hyperventilation has concluded that the primary problem is in fact the ventilation *variability* as opposed to the absolute CO_2 level (30). This was indirectly supported by the absence of a significant correlation between P_{capCO2} and NQ score in the study.

Because many hyperventilation symptoms seem to stem from sudden increases in the systemic pH value, the pH-compensated state of CIH patients may in fact produce fewer symptoms. However, this does not suit the observation that CIH patients in average display a degree of breathlessness and quality of life that is comparable with patients with severe COPD (2, 5). It is very possible that many CIH patients *also* suffer from an unstable respiration, their P_{aCO2} varying within the hypocapnic range.

Based on the recent findings in several studies that the act of normalizing CO_2 produces a significant treatment benefit in asthma, anxiety and other disorders (7–10, 20, 21), further research should be carried out in the possibility of *user-passive* treatments for normalizing blood gas levels and alveolar ventilation. Such a treatment might allow a larger number of patients to be treated, not just restricting the benefits to the minority of patients with the significant discipline and self-control needed to successfully carry out a rigorous and demanding breathing retraining.

Also, this kind of device would be very beneficial in acute hyperventilation attacks in order to quickly and effectively stabilize blood gas values and pH.

Acknowledgements

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