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Conclusions: Our pilot intervention provided evidence for the feasibility of pCO2-biofeedback training in asthma patients.

Response to Reviewers: Dear Dr. Gevirtz,

Thank you for the latest comments on our manuscript “Targeting PCO2 in asthma: Pilot-evaluation of a capnometry-assisted breathing training” (APBI55). We have now amended the manuscript by following the reviewrs suggestions in the remaining details. The amended passages are marked in yellow.

Thank you for the opportunity to have our work reviewed for your journal. We are excited that it has generated sufficient interest among our reviewers and look forward to seeing it in press.

Please let us know if you need more information or materials.

Sincerely,

Alicia E. Meuret, Ph.D.

TARGETING PCO2 IN ASTHMA:

PILOT EVALUATION OF A CAPNOMETRY-ASSISTED BREATHING TRAINING

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ABSTRACT

Objectives: This pilot study aimed to evaluate the feasibility and potential benefits of a novel biofeedback breathing training for achieving sustained increases in pCO2 levels.

Methods: Twelve asthma patients were randomly assigned to an immediate 4-week treatment group or waiting list control. Patients were instructed to modify their respiration in order to change levels of end-tidal pCO2 using a hand-held capnometer. Treatment outcome was assessed in frequency and distress of symptoms, asthma control, lung function, and variability of peak expiratory flow (PEF).

Results: We found stable increases in pCO_2 and reductions in respiration rate during treatment and 2-month follow-up. Mean pCO_2 levels rose from a hypocapnic to a normocapnic range at follow-up. Frequency and distress of symptoms was reduced and reported asthma control increased. In addition, mean PEF variability decreased significantly in the treatment group.

Conclusions: Our pilot intervention provided evidence for the feasibility of pCO_2-biofeedback training in asthma patients.

Keywords: Asthma; hypocapnia; breathing training; pCO_2; biofeedback

Abbreviations:

pCO_2: maximum partial pressure of CO2

f_R: respiration rate per minute

FEV1: forced expiratory volume in the first second

FVC: forced vital capacity

R_{int}: interrupter resistance

PEF: peak expiratory flow

Alternative and complementary interventions for asthma have attracted considerable attention in recent years (Wright, 2004). Among these, interventions targeting breathing behavior have been recommended as adjunctive treatments for some time. However, little empirical evidence is currently available in support of the efficacy of various forms of breathing training (Ernst, 2000; Holloway & Ram, 2004; Ritz & Roth, 2003). This is surprising because a number of these methods, such as nasal breathing, pursed-lip breathing, hypoventilation, or respiratory muscle relaxation, are based on valid psychophysiological rationales (Ritz & Roth, 2003). One recent trial of breathing training teaching slow, regular and abdominal breathing to reduce potential hyperventilation showed positive effects on patients' quality of life (Thomas, McKinley, Freeman, et al., 2003). However, no physiological measurements were reported that would have confirmed successful manipulation of breathing patterns or treatment effects on lung function. Another breathing training method that promotes a reduction in hypocapnia directly by slow and shallow breathing and breath-hold exercises has generated more systematic research in controlled intervention studies. Originally developed by the Russian physician Buteyko (Stalmatski, 1997), the technique is based on the idea that asthma exacerbations are caused by chronic hypocapnic breathing, and that retraining of patients' breathing pattern to achieve a long-term reduction in ventilation will result in an improvement in asthma control. Recent controlled trials of this technique reported reductions in medication (in particular β-adrenergic bronchodilators) and improvements in quality of life of the patients (Browler, Green, Mitchell, 1998; Cooper, Oborne, Newton, et al., 2003; Opat, Cohen, Bailey, et al., 2000; McHugh, Aitcheson, Duncan, et al., 2003).

It has been known for some time that hypocapnic hyperventilation exacerbates asthma (Herxheimer, 1946). Experimental studies have demonstrated a decline in lung function when carbon dioxide partial pressure (pCO_2) is reduced (Newhouse, Becklake, Macklem, et al., 1964; van den Elshout, van Herwaarden, & Folgering, 1991; Sterling, 1968). Also, lower

pCO_2 levels have been linked to airway hyperresponsiveness in asymptomatic asthma patients (Osborne, O'Connor, Lewis, et al., 2000). Excessive ventilation without hypocapnia is a key mechanism in the development of bronchospasm in asthma and has been suggested to explain exercise-induced bronchoconstriction (McFadden & Gilbert, 1994). Repeated excessive ventilation with cold dry air has also been shown to result in increases in airway hyperresponsiveness, inflammation and in impairments in response to ß-adrenergic bronchodilators in an animal model (Davis & Freed, 2001; Davis, Schofield, & Freed, 2003). There is evidence for basal ventilatory states or ventilatory responses that put asthma patients at greater risk of exacerbations. While oxygen saturation is usaully normal in asthma patients except for periods of severe exacerbation (Wagner, Hedenstierna, & Rodriguez-Roisin, 1996)), studies have found lower resting pCO_2 in patients than in healthy controls (Hombrey et al., 1988; Osborne, O'Connor, Lewis, et al. 2000; Ritz, Wilhelm, Meuret, & Roth, 2003) or stronger minute ventilation or respiratory drive at baseline or in response to exercise (Ritz, Dahme, Wagner, 1998; Varray, Prefaut, 1992), added resistive loads (Kelsen, Fleegler, & Altose, 1979), or methacholine-induced bronchoconstriction (Fujimori et al., 1996). Hypocapnia has also frequently been observed in asthma attacks (McFadden & Lyons, 1968).

While there is some evidence in support of the basic assumptions of the Buteyko breathing technique as an adjunctive treatment for asthma, published controlled trial have provided little evidence that pCO_2 had been targeted successfully (Ritz & Roth, 2003; Bruton & Holgate, 2005; Walters & Johns, 2001). None of the reported trials has shown that respiratory gas exchange can be significantly altered by this type of breathing training. Only one included measurements of pCO_2 and minute ventilation, but significant changes at 4 weeks post-training or 2-months follow-up were only seen in the latter index (Cooper, Oborne, Newton, et al. 2003). Demonstrating that stable pCO_2 levels have been brought into a healthy range is necessary to confirm Buteyko's idea of how his hypoventilation training works (Stalmatski, 1997). Without that, only nonspecific factors may be responsible for the

reported improvements. For example, any therapeutic rationale that strongly emphasizes a reduction in bronchodilator use might well cause patients to report reduction of that use after weeks of training.

Hence, we designed an adjunctive training for asthma patients that directly targets pCO_2 and tested it in a small number of patients. The results would encourage or discourage a more comprehensive clinical intervention trial using hypoventilation training. Feedback of pCO_2-levels can bring them under the voluntary control of the patient, as has been demonstrated with patients suffering from chronic hyperventilation (Folgering, Lenders, & Rosier, 1980; van Doorn, Folgering, & Colla, 1982). In prior research, we successfully developed and tested a capnography-assisted breathing training for reducing hypocapnia in patients with panic disorder (Meuret, Wilhelm, & Roth, 2001, 2004). The technique resulted in elevations of end-tidal pCO_2-levels during laboratory testing over weeks and months. In this study we report the adaptation and pilot testing of this technique in asthma patients. Our main goal was to demonstrate the feasibility of the technique and to provide initial evidence of its efficacy.

METHODS

Participants

Adult asthma patients were recruited by advertisement in local newspapers, online message boards, and posters in medical school departments for a study of breathing training in asthma. The assessment schedule included participation in an initial interview on psychiatric and asthma history, in two laboratory assessments, one 24-hour ambulatory monitoring day, and a 4-week breathing training program with an 8-week follow-up assessment. Potential participants had to be non-smokers between 18 and 60 years old, which reduced the risk of including patients with chronic obstructive pulmonary disease. Further exclusion criteria were use of oral corticosteroids in the previous 3 months, cardiovascular disease,

neurological disorders, clinically significant levels of depression, or life-time diagnosis of schizophrenia, dementia, or psychosis. Patients were also screened for the presence of anxiety disorder, which was not an exclusion criterion, but would potentially add to the interpretation of findings. Twenty-one patients were screened initially, of which 9 (42.9%) had scheduling problems or were not eligible because they did not meet the inclusion criterion. The final 12 patients were randomly assigned to an immediate 4-week treatment group (n=8) or a 4-week waiting list group (n=4). Waiting list patients were offered an identical treatment after the four weeks.

Suitable candidates were invited for medical history taking, which focussed on their asthma, and included lung function testing by spirometry. Patients also filled in a structured questionnaire on various aspects of their disease manifestation and on diagnostic procedures (lung function testing, bronchial provocation tests, allergy tests), for which they had to contact their general practitioner or specialist and ask for documentation. All patients had a present diagnosis of asthma. Only one waiting-list patients reported brief previous contact with training in breathing techniques. Participation was voluntary, and informed consent was obtained from all patients. The study was approved by ethical review committees of the VA Palo Alto Health Care System and Stanford University Medical School.

Instruments and measures

End-tidal pCO_2 was measured with a light (320g), handheld (65 x 128 x 35 mm), battery-operated capnometry device (Capnocount mini, Weinmann, Germany), which analyzes exhaled breath pumped into the device through a nasal cannula (Wilhelm, Alpers, Meuret, et al. 2001). The instrument displays breath-by-breath end-tidal pCO_2 (in mmHg) and respiration rate (f_R) (in breaths/min), and records them with the time and date of the measurement.

Mechanical lung function was measured with an electronic pocket spirometer (Jaeger/Toennies, AM2). The best of three expirations was stored in the electronic memory

of the device together with a volume-time profile that allows for detection of submaximal performance of the maneuver. Forced expiratory volume in the first second (FEV_1) was used as the primary outcome measure. In addition, peak expiratory flow (PEF) and FEV_1 divided by forced vital capacity (FVC) were extracted at the first session. Before spirometry, interrupter resistance (R_{int}; MicroRint, MicroMedical Ltd., UK) was measured and R_{int} was determined as the average of the median of 10 inspiratory and 10 expiratory interruptions. These measurements were taken initially at each of the five training sessions by an investigator who did not conduct the sessions. This measure of respiratory resistance has the advantage of being effort-independent and provides a more direct index of airway constriction (Ritz et al., 2002). Before and after the 4-week treatment and at follow-up, patients recorded their PEF five times daily: in the morning after awakening (before bronchodilator), and at approximately 11am, 2 pm, 5 pm, and 8 pm. A brief tone sequence from the AM2 at those times reminded patients to perform the PEF test. From the 3-day recordings, % PEF variability was extracted as follows (Reddel, Jenkins, & Woolcock, 1999): the morning value before bronchodilator use divided by the patient's personal best value during the 3-day period, multiplied by 100, and subtracted from 100. While peak flow diaries have been shown to be prone to substantial problems with missing values (e.g., Chowienczyk et al., 1994), adherence of patients with this brief protocol was excellent, with the average number of measurements per day being 5.5 (range: 3.7-6.7) at pre-training, 5.3 (4.3-5.7) at post-training, and 4.9 (3.3-5.7) at follow-up (patients often performed additional measures beyond the specified times). Compliance did not change significantly thoughout the observation period, Friedman-Test $\chi(2)=1.3$, $p=.527$.

Questionnaire measures. Initially, patients filled out a set of questionnaires at home, which covered demographics and information on asthma history, symptom patterns, recent health care utilization, medication use, and effect of medication. Patients were asked to rate how effective their current medication was (rating 1-4, "always", "most of the times",

"sometimes", or "never"). At the beginning of each therapy session they filled out a questionnaire on frequency of asthma symptoms and how much distress they had caused ("symptom bother scale") (Steen, Hutchinson, McColl, et al., 1994), and self-report items of the Asthma Control Questionnaire (Juniper, O'Byrne, Guyatt, et al., 1999) for the period of the previous week. At the 1st and 5th session and at follow-up the Health Survey Short Form-12 (Ware, Kosinski, & Keller, 1996) was also administered. Patients undergoing training also filled in the Positive Affect Negative Affect Schedule (PANAS; Watson, Clark & Tellegen, 1988), from which we analyzed the negative affect subscale scale to explore whether the training had a nonspecific effect on patients' negative mood.

After follow-up assessments, patients were given a treatment evaluation sheet, which they were asked to complete at home and to return in a stamped envelope. On the sheet were the following questions (rated from 0 – 10, "not at all" to "extremely"): "How *logical* does this treatment appear to you for helping people with asthma?", "How *confident* are you that this treatment will improve your symptoms of asthma?", "How *confident* are you that this treatment will improve the control you have over your asthma?", "How *confident* would you be to recommend this treatment to a friend with asthma?" "How *successful* do you think this treatment would be in dealing with other problems, for example, headaches or sleeplessness?"

Treatment procedures

General rationale and goal of the training. Our breathing training was offered only as an adjunctive treatment. Patients were advised to continue their regular preventative medication as recommended by their physician at a stable level throughout the 4 weeks of treatment. A clinical psychologist experienced in breathing techniques conducted the treatment sessions on an individual basis. The breathing training rationale cited evidence that hypocapnia and excessive ventilation adversely affect lung function in asthma and can be involved in asthma exacerbations. The training was aimed towards voluntarily increasing self-monitored end-tidal

pCO_2 by reducing f_R and variability in the respiratory pattern (e.g. intermittent deep breaths, sighing) through breathing exercises. It was adapted from a breathing retraining protocol recently developed for panic patients (Meuret, Wilhelm, & Roth, 2001; 2004).

Before treatment, patients underwent a 24-hour ambulatory monitoring of autonomic function (electrocardiogram, electrodermal activity, skin temperature), lung function (spirometry) and respiration (inductance plethysmography, capnography). Recordings of respiration were subsequently used qualitatively in the initial session of the breathing training.

Components of the treatment. The training consisted of five weekly treatment sessions (initial session plus four treatment sessions) of approximately 1 hour duration. The treatment had five major components: (a) educating patients about the role of breathing in asthma exacerbations, (b) directing their attention to their respiratory patterns, particularly those observed in 24-hour monitoring records, (c) having them perform various breathing maneuvers with capnometer feedback to experience how changes in breathing affect physiology and symptoms, (d) teaching them ways to simultaneously control pCO_2 levels, f_R, and tidal volume, (e) and having them practice breathing exercises at home.

Home exercises. An individual home training exercise consisted of three parts: (a) an initial 2-min period, during which patients sat quietly with their eyes closed (b) a 10-min paced breathing period during which patients breathed in synchrony with tones from a tape while trying to increase pCO_2 and decrease f_R using the display of the capnometer for feedback, and (c) a 5-min breathing period without pacing tones during which patients were to maintain their previously paced f_R and pCO_2 level using feedback from the display. Pacing tones started at 13 breaths/min in the first week, and switched to 11, 9, and 6 breaths/min in subsequent weeks. Before and after each exercise patients rated their current symptoms and mood in the electronic diary of the pocket spirometer and then measured their lung function. They also filled in a separate diary sheet with information on medication, prior physical activity, and their observed pCO_2 levels, f_R, and PEF. All instructions and pacing tones for home exercises were given on

standardized pre-recorded audiotapes, and patients were provided with a pocket-sized cassette player. Patients were instructed to gradually adjust their breathing patterns (f_R, rhythm, and depth) though slow, shallow, and abdominal breathing to reach or maintain a pCO_2 level around 40 mmHg. If levels exceeded 45 mmHg, they should reduce their efforts and let levels fall back closer to 40.

Treatment sessions. In the first two weeks the emphasis was largely on stabilization of breathing patterns (f_R and rhythm), while in the last two weeks it was shifted to normalizing pCO_2. For patients with initial pCO_2 levels within the normal range (37 - 40 mmHg; 3 patients in the treatment group, 2 in the waiting list), treatment focused on regularity of breathing to prevent pCO_2 fluctuations. Exercises were to be performed twice a day for 17 min, at home or elsewhere.

In the first session patients were presented a series of charts with information about effects of hyperventilation on lung function and symptoms in asthma, the relationship between symptoms, anxiety, and hyperventilation, and the therapy goals. The weekly hourly sessions began with filling out weekly questionnaires on symptoms and asthma control, followed by 3-min pCO_2 measurements and lung function assessments. Capnometer exercise data recorded during the previous week were then reviewed. The trainer examined individual capnometer print-outs with the patient, looking for evidence of concordance between changes in pCO_2 and f_R and changes in symptoms before and after the exercises. Analysis of exercises was followed by further training with the feedback device. At the end of the session, patients were instructed on how to use the new breathing tapes. The final session concentrated on maintenance of treatment gains.

Patients returned to individual treatment and assessment sessions at the same time of the day ± 2 hour. Those who used higher doses of bronchodilator medication were encouraged to reduce those doses and practice the breathing maneuvers as long as symptoms were still tolerable. At the 5^{th} treatment session, the pacing tapes and capnometer were collected from

the patients, who were encouraged to continue applying the breathing techniques whenever they found them helpful.

Waiting list condition. Waiting-list patients were asked to start treatment after a period of 4 weeks. They received the same assessment of PEF variability, basal pCO_2, lung function, asthma symptoms, and health status as the immediate treatment patients. Following the waiting-list period, two patients chose to participate in the training, while two others had either scheduling problems or an asthma exacerbation requiring oral corticosteroids.

Data analysis

Because the size of the control group was small, we limited inferential statistics to the treatment group and used control group means for qualitative comparison only. Treatment effects were analyzed with one-way repeated measures ANOVAs with pre-treatment, post-treatment, and follow-up as three time points. Where the sphericity assumption was violated, significance levels were corrected using the Geisser-Greenhouse epsilon. In those cases, we report the original degrees of freedom and the corrected significance levels. Bronchodilator use (item 6 of the asthma control questionnaire) was analyzed using the nonparametric Freedman rank test due to a lack of normal distribution. Post-hoc comparison of post-treatment and follow-up with pre-treatment means used the Newman-Keuls procedure.

RESULTS

Patient characteristics

Patients in the treatment group were predominantly married women, Caucasian (beyond that, 1 woman reported being 80% African American, 20% Native American, and 1 woman 100% Asian/Pacific Islander), currently employed, and well educated (on average 17 years) (Table 1). Five treatment patients (62.5%) reported onset of asthma before the age 18 years. Control patients were mostly comparable, but were younger and 2 (50%) were Non-Caucasian (1 woman 50% Spanish 50% Tunesian, 1 man 100% Hispanic). Patients had mainly mild intermittent to moderate persistent disease severity; with 50% treatment and 25% control patients

reporting daily symptoms. Daily activities were affected every day in 2 (25%) treatment and 1 (25%) control patient. Nighttime symptoms at least up to 2 times per month were reported by 6 (75%) treatment and 2 (50%) control participants. All patients reported that their medication helped against shortness of breath "most of the time", while 1 treatment (12.5%) and 1 control patient (25%) reported that it helped against cough and wheezing only "sometimes" or "never". Patients reported only up to one emergency treatment in the previous year, with proportionally more controls patients reporting such incidences (see Table 1). Also, FEV_1/FVC was somewhat lower in the control group. The beginning of treatment was distributed across one year (one patient in January, one in March, two in April, one in May, one in August, one in September, and one in November), while two waiting-list patients were enrolled in May, and two in October. Most patients except for one in the treatment and one in waiting-list group reported having asthma symptoms typically in more than one season. One patient reported having had panic attacks in the past, but did not have any attacks during treatment or follow-up.

Treatment outcome

Evidence of manipulation success: End-tidal pCO_2 and respiration rate. The treatment resulted in significant pCO_2 increases and f_R decreases that were stable through follow-up, as shown by mean values recorded at the beginning of the first and last treatment and follow-up session (Table 2). Data from individual patients showed pCO_2 values at follow-up that were higher than at pre-treatment in all participants of the treatment group, and respiration rate dropped substantially in five participants (Figure 1). Waiting-list patients remained mostly stable. One participant had rather high pCO_2-levels (50 mmHg) at post-treatment measurements, but showed more moderate levels (42.7 mmHg) at follow-up. Also, inspection of his records during the 4th training week showed that the maximum pCO_2 values he had reached during individual exercises ranged from 40 to 44 mmHg.

Treatment adherence. None of the recruited patients ended their participation in the trial prematurely. Of the required 13 weekly home exercises, patients completed 11.3 ± 2.7, 13.0 ±

1.1, 12.6 ± 1.8, 11.3 ± 4.1 home exercises, for the 1st, 2nd, 3rd, and 4th week, respectively. Some patients performed one additional exercise and one of them 3 additional exercises in one week. Only one patient showed a low compliance during the 4th week of the training with a total of 3 home exercises.

Questionnaire measures. Significant decreases in frequency of symptoms and distress by symptoms were reported in the treatment group (Table 2). At the same time, self-reported asthma control increased. General health status measured by the SF-12 and negative affects measured by the PANAS remained unchanged.

Lung function. Basal lung function with regard to FEV_1 and R_{int} remained stable. On the other hand, PEF variability fell through follow-up. Individual values suggested a rather uniform decrease in symptoms and PEF variability for treatment patients (Figure 2).

Medication. All patients except for one in the treatment group remained on a stable level of preventative medication during the four weeks of treatment. This patient increased his inhaled corticosteroid dose in the 4th week due to a cold. He then discontinued all medication for the 8 weeks leading up to follow-up assessments, and reported being able to control symptoms (which were mainly cough) usually within one minute using breathing techniques. Recalculating the analyses without this patient did not change findings substantially. At follow-up one more patient had discontinued all medication, and one had reduced the inhaler corticosteroid dose, while one patient had been prescribed additional leukotriene inhibitor medication, and for one, the leukotriene inhibitor had been replaced by an inhaled corticosteroid. Preventative medication levels remained stable in waiting-list patients.

On average, bronchodilator use remained unchanged, at rather low levels. Initially, only four patients in the treatment group reported bronchodilator use, and none in the control group. After four weeks, three treatment patients had increased their use or started use, while three had decreased their use. Two patients in the control group had started to use their bronchodilators after the 4 weeks on waiting list. At follow-up, four treatment patients had

decreased, and one increased their use. One patient reported having had a cold-induced exacerbation a few weeks before the follow-up assessments, which had required an increase in bronchodilator doses. She reported no benefits of breathing exercises for these symptoms, but thought that the exercises had speeded up recovery from her asthma exacerbation.

Patients' treatment evaluation

Five patients in the treatment group returned their evaluation sheets. Most of them found the treatment rationale logical (ratings >= 7; mean = 7.2, range 5 - 9); only one patient found it "somewhat logical". On average, patients were confident that it would enable them to control their symptoms (mean = 6.6, range 2-10) and control their asthma (mean = 6.0, range 2-10). They were likely to recommend the training to a friend (mean = 7.2, range 5-10), and thought it may be helpful for other diseases as well (mean = 6.8, range 5-9). The two control patients participating in the training after the waiting period also returned their forms and showed evaluations closely matching these, with ratings between 5 and 10 on individual scales.

DISCUSSION

In this pilot-study we tested a new breathing training with capnometer feedback to increase asthma patients' pCO_2 levels. We found stable increase in pCO_2 across an 8-week follow-up period in patients trained with this method. Prior studies attempting to train hypoventilation did not attempt to measure changes in this key parameter or were not able to demonstrate substantial changes (Browler, Green, & Mitchell, 1998; Cooper, Oborne, Newton, et al., 2003; Opat, Cohen, Bailey, et al., 2000; McHugh, Aitcheson, Duncan, et al., 2003). Compared to other methods our training had the advantage of allowing for an immediate manipulation check by the patient and a systematic evaluation of pCO_2-changes by the therapist. The feedback of a key physiological parameter increases the plausibility of the training and rewards the patient for successful breathing change. Electronic storage of the data allows a review of exercises and serves as an important element in increasing patients' compliance with

the home training schedule. Using an electronic spirometer with diary function, our home training relied strongly on electronic recording techniques, which have become state-of-the art in ambulatory and self-management studies with asthma patients (Chowienczyk, Parkin, Lawson, et al., 1994; Milgrom, Wamboldt, & Bender, 2002; Ritz & Steptoe, 2000). Future evaluations of this training could be enhanced by additional electronic monitoring of medication usage (Berg, Dunbar-Jacob, & Rohay, 1998).

These initial results also suggest benefits of the training on patients' asthma control. Frequency and distress of symptoms was reduced, and asthma control increased, over the weeks leading up to follow-up assessments. Lung function remained stable, although decreases were seen in respiratory resistance that might have been significant with a larger sample size. A greater sensitivity of these more direct measures of airway obstruction to the effects psychosocial interventions has been observed before (Lehrer, Vaschillo, Vaschillo, et al., 2004; Ritz, Dahme, DuBois, et al., 2002).

We also observed a substantial decrease in variability of lung function across weeks to below values typically used as criteria of asthma diagnosis (NHLBI, 2003). Thus, improvement through training extended beyond patients' perception of their disease to a somatic outcome measure central to the pathophysiology of asthma. Although the relationship between PEF variability and airway hyperresponsiveness has been debated (Douma, Kerstjens, Roos, et al., 2000; Reddel, Salome, Peat, et al., 1995), such findings are compatible with prior findings of a negative correlation between pCO_2 and hyperresponsiveness to methacholine challenge (Osborne et al., 2000). It is likely that additional benefits of an adjunctive breathing training will be less apparent in basal lung function (or only be visible in more direct measures of airway obstruction) than in a reduction of fluctuations in symptoms. At follow-up, in addition to reduction in symptoms and greater asthma control through questionnaires, two patients also reported that they felt improvements in their ability to control symptoms and to recover from asthma exacerbation. Although spirometric indices of lung function are typically dependent on

patients' effort (Ritz et al., 2002), we do not think that the observed reductions in PEF variability could easily be explained by this factor. Complicated and less plausible assumptions would have to be invoked to explain this finding, such as a reduction in the inconsistency in patients' effort due to therapy. Given the particular index we chose for PEF variability, which contrasts lowest morning values with the maximum value during the measurement period (Reddel et al., 1999), this assumed reduction in inconsistency, would also have to be specific to certain times of the day.

Because our sample was not selected for high levels of severity or low asthma control, we may have been less able to show substantial changes in some of the outcome variables. On average, initial lung function was close to 100% of predicted, and bronchodilator medication use was low. Studies of the Buteyko technique have especially demonstrated reductions at high levels of bronchodilator use. Reductions are important, but assessment by self-report has limitations (Berg, Dunbar-Jacob, & Rohay, 1998). It is not surprising that an intervention that stresses reduction in reliever medication as an important goal leads patients to report such reductions at the end of the training, at least in part because patients have some decision latitude in the level of usage of this medication for symptoms. Future trials may profit from inclusion of more severe cases of asthma or patients with overuse of bronchodilator medication.

The range of applicability of hypoventilation training for asthma patients remains to be determined. Although excessive minute ventilation and low pCO_2 are often reported in asthma (Osborne, O'Connor, Lewis, et al. 2000; Ritz, Dahme, & Wagner, 1998; Varray & Prefaut, 1992, Kelsen, Fleegler, & Altose, 1979), a sizable number of patients show normal or close to normal levels of pCO_2. The target for such patients can be stabilization of normal levels of pCO_2 by more regular breathing. However, little is known about the importance of variability of breathing patterns in daily life for asthma symptoms. Highly variable breathing patterns with intermittent deep breaths (sighs) are often observed in panic patients (Abelson, Weg, & Nesse, 2001; Wilhelm, Gerlach, & Roth, 2001) and could lead to maintenance of low pCO_2 levels.

Intermittent deep inspirations dilate the airways and decrease hyperresponsiveness of the airways, but may also lead to bronchoconstriction in more severe asthma (Fish, Ankin, Kelly, et al., 1981; Lutchen, Jensen, Atileh, et al., 2001). In our study, three patients with high initial pCO_2 levels showed only small increases from pre-treatment (39.0 ± 1.1 mmHg) to post-treatment (39.6 ± 3.1 mmHg) and follow-up (41.6 ± 1.9 mmHg), and further qualitative inspection of their means in outcome variables suggested lower initial symptom scores (1.1 ± 0.3 vs. 1.5 ± 0.6) and PEF variability (13.2 ± 6.7 vs. 32.9 ± 14.5 %), combined with smaller reductions across training than in the 5 patients starting with lower pCO_2 levels (31.7 ± 2.4 mmHg). Although patients were relatively positive in their final evaluation of the training, measurable benefits of the training in terms of asthma control may be restricted to patients in the hypocapnic range.

Our breathing training was originally developed to correct hypocapnic breathing patterns in patients with panic disorder (Meuret, Wilhelm, & Roth, 2001). In a recent clinical trial we demonstrated substantial reductions in panic symptomatology over a 1-year period (Meuret, Wilhelm, Ritz, et al., under review) in these patients. Asthma patients are more likely than the general population to also suffer from panic disorder (Carr, 1998; Hasler, Gergen, & Kleinbaum, 2005; Ritz, Thoens, Fahrenkrug, et al., 2005), and emotion-induced overbreathing has been observed in asthma patients (Clarke & Gibson, 1980), particularly in anxious states surrounding asthma attacks. Panic-fear has been linked to suboptimal management of asthma, such as greater use oral corticosteroid (Hyland, Kenyon, Taylor, et al., 1993; Kinsman, Spector, Shucard, et al., 1974; Ritz, Bobb, Edwards, et al., 2001). Thus, an additional benefit of the training could lie in teaching of skills to reduce comorbid panic, particularly the risk of panic-induced overbreathing in the event of severe asthma symptoms.

Our current findings do not allow disentangling effects of slow breathing training from effects of systematic biofeedback-induced increases in pCO_2. Slow breathing training has been shown to be beneficial in cardiovascular disease (Bernardi, Spadacini, Bellwon, et al., 1998; Schein, Gavish, Herz, et al., 2001), probably due to its potential to increase baroreflex

sensitivity (Bernardi, Porta, Spicuzza, et al., 2002; Joseph, Porta, Casucci, et al., 2005). However, little is know about changes in breathing pattern or slow breathing alone in asthma (Ritz & Roth, 2003). Recent research combining slow breathing with heart rate variability biofeedback has demonstrated beneficial effects on lung function and steroid medication needs in asthma (Lehrer, Vaschillo, Vaschillo, et al., 2004), as well as symptomatic and functional improvements in chronic obstructive pulmonary disease (Giardino, Chan, Borson, et al., 2004), but mechanisms behind such effects are largely unexplored. Although improvements in oxygen saturation have been observed for typical breathing frequencies (6-8 breaths/min) employed by such studies (see also Bernardi et al., 1998), these effects cannot easily explain changes in mechanical lung function, such as in basal respiratory resistance (Lehrer et al., 2004), or PEF variability, as observed in the present study. Future studies need to address the relative importance of various breathing maneuvers in respiration-oriented interventions and pathways through which they can affect organic disease manifestations.

Our study was clearly limited in its sample size and its lack of a control group large enough for meaningful inferential statistics. However, our main goal was to pilot-test the feasibility and benefits of this newly developed training. The substantial increases we observed in pCO_2 across training are difficult to attribute to nonspecific factors such as attention or mere temporal fluctuations. Although qualitative comparison with the control group suggested superiority of the intervention, nonspecific factors may have contributed to the improvements. Greater awareness of the disease and our requirements to continue regular medication may have resulted in an improved asthma self-management. In addition, expectancy of improvement generated by the treatment rationale may have impacted on self-report of symptoms and asthma control, but improvement in PEF variability would be difficult to explain by such effects. Also, the lack of changes in negative affect throughout the observation period argue against nonspecific effects through anxiety reduction, which might be invoked as an explanation derived from the original application of the pCO_2 biofeedback training to panic patients (Meuret et al.,

under review). Future studies will have to implement comparison interventions that follow monitoring protocols controlling closely for the amount of self-attention, attention directed to the patient by the therapist, and expectancy of improvement by the patient.

CONCLUSION

Our pilot intervention has provided initial evidence for the feasibility of 4-week pCO_2-biofeedback training in asthma patients. Stable increases in pCO_2 can be achieved by a combination of five expert-guided sessions and daily home exercises using slow paced breathing and feedback of actual pCO_2-levels. The training allows for a more direct test of the assumptions underlying breathing interventions such as the Buteyko technique, because it targets directly the basic physiological parameter of the pathophysiological rationale of the technique. The training was well tolerated by our patients and reduced symptoms and variability of PEF. We therefore recommend a more thorough investigation of its benefits as an adjunctive behavioral self-management technique for asthma patients.

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Table 1. Demographics and asthma-related variables among patients in immediate treatment and waiting list conditions

	Treatment (*n*=8)	Wait-list control (*n*=4)
Patient characteristics		
Gender, women (%)	75.0	75.0
Age in years (mean, range)	43.5 ± 11.0	34.0 ± 15.5
Ethnicity, White Caucasian (%)	75.0	50.0
Family and educational background		
Married (%)	87.5	50.0
Years of education	17.0 ± 1.9	17.3 ± 2.5
Currently working (%)	75.0	75.0
Asthma characteristics		
Age of asthma onset, years, (mean ± SD)	18.1 ± 15.9	17.0 ± 15.4
Family history of asthma and/or allergies positive, (%)	75.0	75.0
Skin test for allergy, positive (%)	100	100
Frequency of symptoms, rating 1-4, (mean ± SD)	2.1 ± 1.0	1.5 ± 1.0
Limitation of daily activities, rating 1-4, (mean ± SD)	2.0 ± 0.8	1.5 ± 1.0
Night time symptoms, rating 0-4, (mean ± SD)	1.8 ± 1.5	1.0 ± 1.4
Asthma care		
Short-acting bronchodilators (%)	87.5	50.0
Long-acting bronchodilators (%)	25.0	50.0
Inhaled corticosteroids (%)	87.5	100.0
Leucotriene inhibitors (%)	50.0	50.0
Anti-histaminics (%)	12.5	50.0
Mast cell stabilizers (%)	25.0	0.0
Effective for short of breath, rating 1-4, (mean ± SD)	2.0 ± 0.0	2.0 ± 0.0
Effective for cough, rating 1-4, (mean ± SD)	2.1 ± 0.4	3.0 ± 1.4
Effective for wheezing, rating 1-4, (mean ± SD)	1.9 ± 0.6	2.7 ± 1.2
Emergency treatment, frequency previous year (%)	12.5%	50%
Lung function		
PEF % predicted (mean ± SD)	99.3 ± 16.8	103.1 ± 18.7
FEV_1/FVC (mean ± SD)	0.82 ± 0.11	0.62 ± 0.18

Table 2. Manipulation success and treatment outcome variables among patients in immediate treatment (n=8) and waiting list (n=4) conditions

	Pre-Treatment	Post-Treatment[§]	Follow-up[§]	Time effect for df=2,14[$]	Effect size d
End-tidal pCO_2					
Treatment	34.4 ± 4.3	38.5 ± 5.8*	40.3 ± 2.6**	F=8.71, p=.011	1.83
Waiting-list	35.9 ± 4.2	35.3 ± 3.9			
Respiration Rate					
Treatment	15.1 ± 3.9	10.0 ± 3.6*	8.9 ± 4.9**	F=6.79, p=.030	0.81
Waiting-list	16.3 ± 4.1	16.4 ± 3.4			
Asthma Symptoms					
Treatment	1.3 ± 0.5	0.8 ± 0.5**	0.4 ± 0.3**	F=14.03, p<.001	1.29
Waiting-list	0.6 ± 0.4	0.6 ± 0.5			
Asthma Symptom (Distress)					
Treatment	1.1 ± 0.6	0.6 ± 0.7**	0.5 ± 0.5**	F=7.34, p=.007	0.89
Waiting-list[+]	0.6 ± 0.3	0.9 ± 0.4			
Asthma Control[#]					
Treatment	1.3 ± 0.9	1.0 ± 0.8	0.5 ± 0.4*	F=5.45, p=.021	1.01
Waiting-list	0.8 ± 0.8	0.9 ± 0.8			
FEV_1					
Treatment	2.33 ± 0.47	2.32 ± 0.33	2.36 ± 0.46	F=0.05, p=.857	0.07
Waiting-list	2.24 ± 0.73	2.53 ± 0.42			
R_{int}					
Treatment[++]	0.49 ± 0.18	0.44 ± 0.10	0.39 ± 0.10	F =1.53, p=.257	0.51
Waiting-list[+]	0.42 ± 0.20	0.42 ± 0.17			
PEF Variability (%)					
Treatment	25.5 ± 15.4	19.8 ± 12.2*	18.2 ± 11.4*	F =4.41, p=.035	0.78
Waiting-list	17.6 ± 14.8	22.0 ± 20.3			

[§] significant difference from pre-treatment values: * p<.05, **p<.01

[$] Time effect for treatment group (n = 8) only

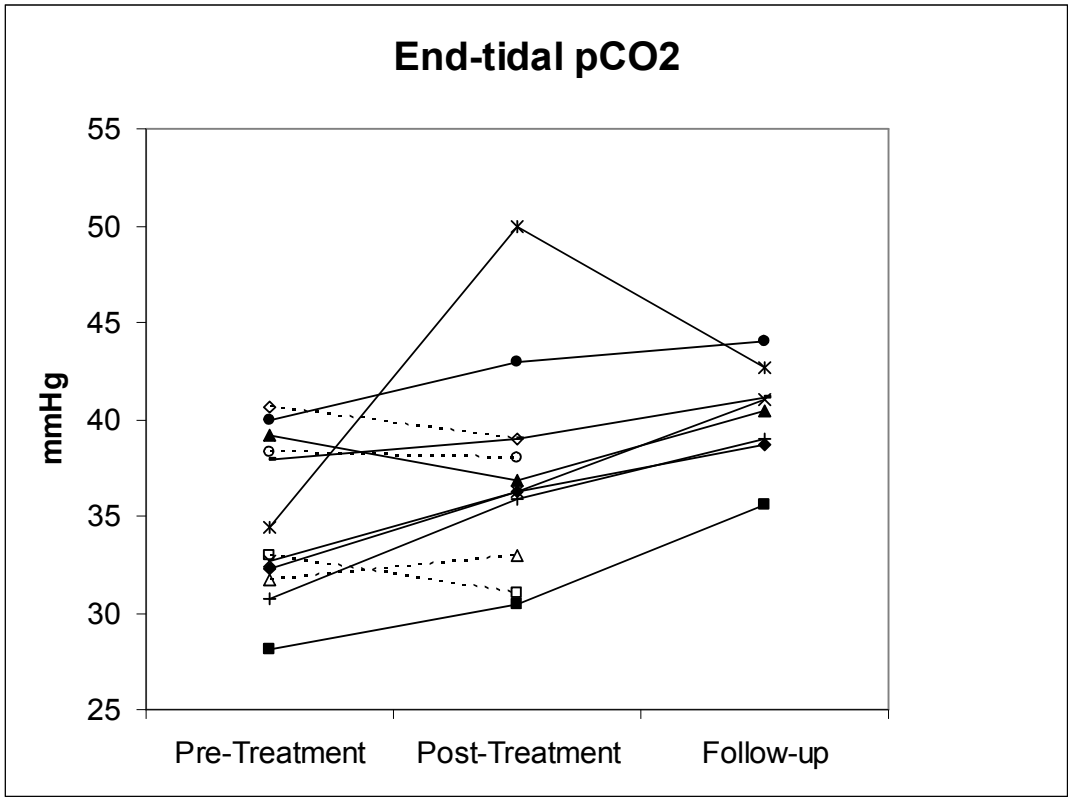
[#]Scoring direction: lower values equals higher control

[+] n = 3 [++] n=7Figure Legends

Figure 1. End-tidal pCO2 (a) and respiration rate (b) across pre-treatment, post-treatment, and follow-up measurements in 8 asthma patients participating in pCO2-biofeedback assisted breathing training

Figure 2. Treatment outcome in asthma symptoms (a) and PEF variability (b) for 8 asthma patients participating in pCO2-biofeedback assisted breathing training

Figure 1 a,b


End-tidal pCO2
55
50
45
40
35
30
25
mmHg
Pre-Treatment
Post-Treatment
Follow-up

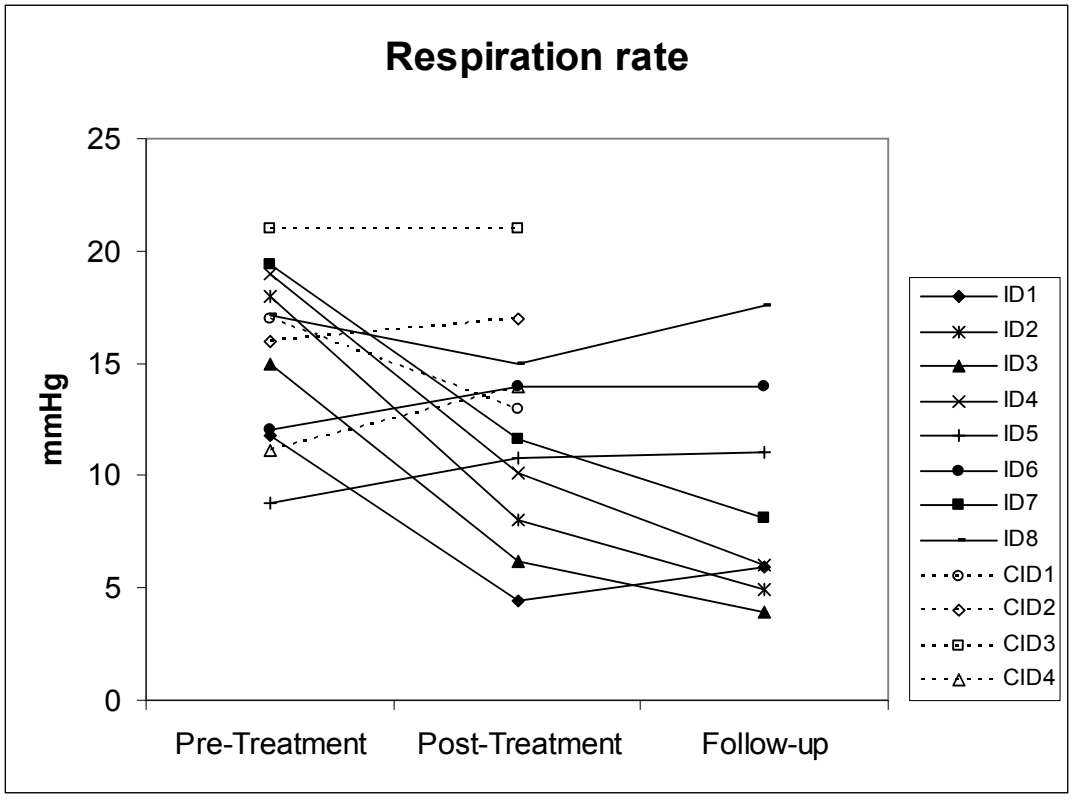
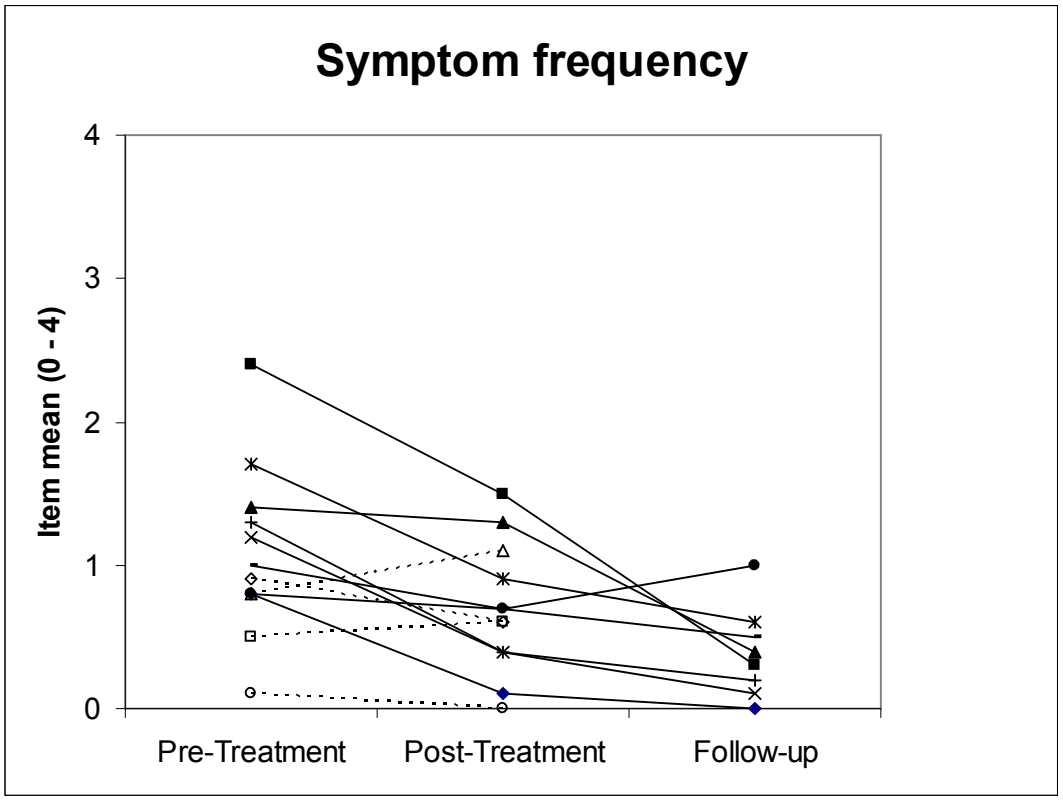
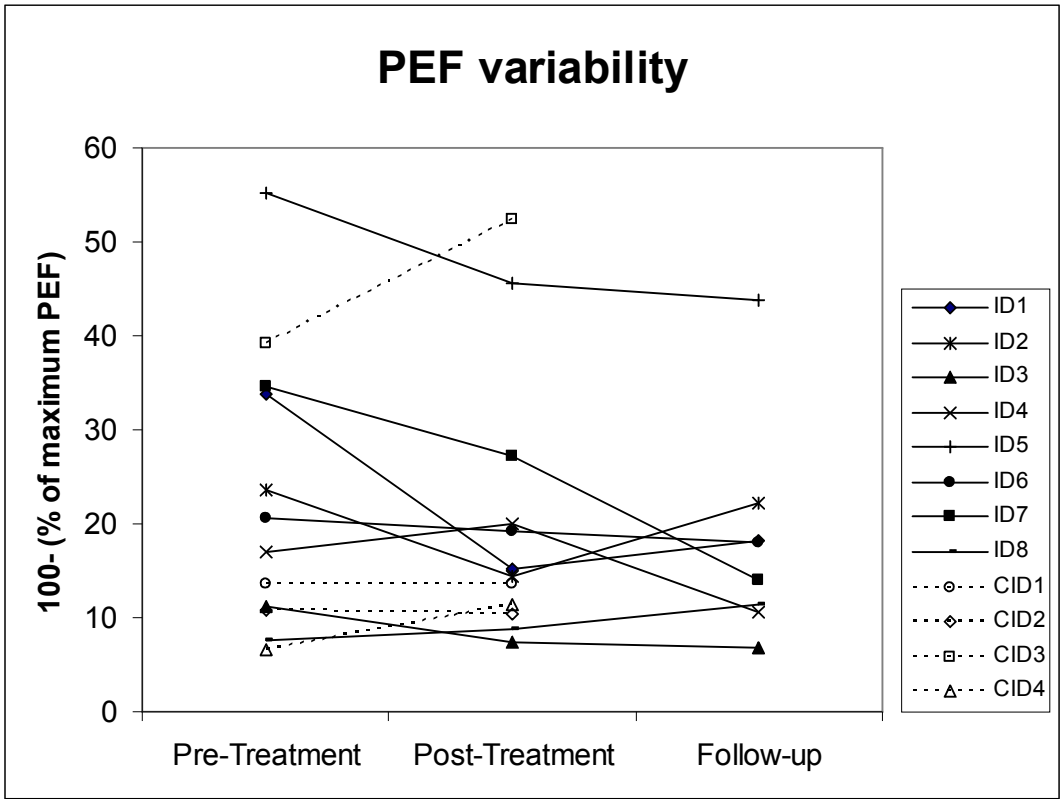

Respiration rate
25
20
15
10
5
0
mmHg
Pre-Treatment
Post-Treatment
Follow-up
ID1
ID2
ID3
ID4
ID5
ID6
ID7
ID8
CID1
CID2
CID3
CID4

Figure 2 a,b


Symptom frequency
Item mean (0 - 4)
4
3
2
1
0
Pre-Treatment
Post-Treatment
Follow-up


PEF variability
100- (% of maximum PEF)
60
50
40
30
20
10
0
Pre-Treatment
Post-Treatment
Follow-up
ID1
ID2
ID3
ID4
ID5
ID6
ID7
ID8
CID1
CID2
CID3
CID4