Appl Psychophysiol Biofeedback (2009) 34:1–6
DOI 10.1007/s10484-008-9070-1

Changes in pCO_2, Symptoms, and Lung Function of Asthma Patients During Capnometry-assisted Breathing Training

Thomas Ritz · Alicia E. Meuret · Frank H. Wilhelm · Walton T. Roth

Published online: 2 December 2008

Abstract In a recent pilot study with asthma patients we demonstrated beneficial outcomes of a breathing training using capnometry biofeedback and paced breathing assistance to increase pCO_2 levels and reduce hyperventilation. Here we explored the time course changes in pCO_2, respiration rate, symptoms and lung function across treatment weeks, in order to determine how long training needs to continue. We analyzed in eight asthma patients whether gains in pCO_2 and reductions in respiration rate achieved in home exercises with paced breathing tapes followed a linear trend across the 4-week treatment period. We also explored the extent to which gains at home were manifest in weekly training sessions in the clinic, in terms of improvement in symptoms and spirometric lung function. The increases in pCO_2 and respiration rate were linear across treatment weeks for home exercises. Similar increases were seen for in-session measurements, together with gradual decreases in symptoms from week to week. Basal lung function remained stable throughout treatment. With our current protocol of paced breathing and capnometry-assisted biofeedback at least 4 weeks are needed to achieve a normalization of pCO_2 levels and reduction in symptoms in asthma patients.

T. Ritz (✉) · A. E. Meuret
Department of Psychology, Southern Methodist University, 6424 Hilltop Lane, Dallas, TX 75205, USA
e-mail: tritz@smu.edu

F. H. Wilhelm
University of Basel, Basel, Switzerland

W. T. Roth
Stanford University School of Medicine and the VA Palo Alto Health Care System, Stanford, USA

Keywords Asthma · Hyperventilation · pCO_2 · Biofeedback · Asthma symptoms

Introduction

Hyperventilation has been known a risk factor for airway obstruction in asthma patients for some time (Herxheimer 1946). Hyperventilation is breathing in excess of the metabolic demand, which leads to respiratory alkalosis characterized by low levels of pCO_2 levels in the blood, alveoli or exhaled air. The patient may experience uncomfortable physical symptoms such as dizziness, dyspnea, and paresthesias (Fried 1993; Wientjes 1992). Reducing pCO_2 levels experimentally can lead to substantial reductions in lung function (Butler et al. 1960; O'Cain et al. 1979; van den Elshout et al. 1991; Sterling 1968). Baseline levels of pCO_2 are often lower in asthma patients than controls (Hormbrey et al. 1988; Osborne et al. 2000) and in one study of mild asymptomatic asthma, lower levels of pCO_2 were related to greater nonspecific airway hyperreactivity (Osborne et al. 2000). Furthermore, hyperventilation symptoms in asthma patients are linked to a lower perceived general health (Ritz et al. 2008b). It has been suggested that hyperventilation acts as a possible mechanism that mediates emotion-induced asthma episodes (Clarke and Gibson 1980; Ritz et al. 2008a).

Consequently, behavioral interventions have been developed to reduce patients' tendency to hyperventilate (Bruton and Lewith 2005), but none of the previously available techniques targeted pCO_2 levels directly or managed to raise them (Bruton and Holgate 2005; Ritz and Roth 2003). This motivated us to adapt and test a capnometry-biofeedback assisted breathing training for patients with asthma (Meuret et al. 2007) that had been

applied before in panic patients (Meuret et al. 2001, 2004), where it was effective both in reducing pCO_2 levels and panic symptoms (Meuret et al. 2008). The training comprised five weekly 1-h therapist-guided training sessions along with home work exercises performed twice-daily home using a portable capnometry device. The goal of these exercises was to reduce overall ventilation and increase tonic pCO_2 to a normocapnic levels. Results of our pilot study with asthmatic patients showed substantial increases of pCO_2 across treatment and 2-months follow-up, together with increases in asthma control and reductions in symptoms and variability of lung function. Basal lung function remained unaffected by the intervention (Meuret et al. 2007).

While our previous analysis demonstrated significant increases in pCO_2 and improvement in asthma symptoms at the end of treatment, we were not sure whether the improvement was gradual or immediate. The course of change (e.g., whether substantial gains took place in some but not all weeks) is of particular importance for future treatment implementations: If less than 4 weeks of training is sufficient to reach substantial increases in pCO_2, the duration of the training could be reduced. A similar conclusion might be drawn if outcome variables such as asthma symptoms change maximally in early stages of the training and less in later stages. Early improvement in psychosocial interventions has implications about how treatments worked (Tang and DeRubeis 1999; Hofmann et al. 2006). To answer questions like these, we analyzed week-by-week changes that asthma patients achieved in pCO_2 and respiratory frequency (f_R) during home exercises and training sessions of the intervention, as well as subsequent change in the key asthma outcome variables weekly symptoms and lung function.

Methods

Methods of the study were presented in detail in our earlier publication (Meuret et al. 2007). In short, the present analysis is based on eight asthma patients (six females; mean age = 43.5 years, SD = 11.0) who were assigned randomly to the immediate treatment group. Patients had mild to moderate asthma according to NHLBI/WHO (1997) criteria and were asked to remain on the same doses of their regular preventative medication for the duration of the study.

Treatment

The 4-week treatment, which was offered as an adjunct, was aimed towards increasing end-tidal pCO_2 and maintaining it in a normocapnic range ($pCO_2 > 37$ mm Hg) by breathing slower, shallower, and less variably. Patients were educated about the role of breathing in asthma exacerbations and what their own habitual breathing patterns were. They were instructed to perform 17-min breathing exercises using the portable capnometer with an electronic display of breath-by-breath end-tidal pCO_2 (in mmHg) and f_R (in breaths/min). Each exercise started with a 2-min baseline period (quiet sitting, eyes closed) and was followed by 10 min of paced breathing at different f_R (13, 11, 9, 6 breaths/min, for weeks 1–4). Patients were instructed to breathe at the target f_R while simultaneously tracking and increasing their pCO_2 levels as fed back to them on the capnometer display. This phase was followed by a 5-min transfer period (no pacing tones) during which levels were to be maintained. For patients with initial pCO_2 levels within the normal range (three patients), the intervention stressed reducing the variability of the breathing pattern to prevent pCO_2 fluctuations. Data collected in the previous week during home exercises were then downloaded from the capnometer and reviewed by the trainer and the patient. Compliance was high with 11.3, 13.0, 12.6 and to 11.3 exercises averaged across patients per week.

Assessments

End-tidal pCO_2 (mm Hg) was measured and recorded with a capnograph originally designed for ambulatory emergency medicine applications (Capnocount mini, Weinmann, Germany; Meuret et al. 2005). Samples of the exhaled breath were taken through a nasal cannula and analyzed in the infrared chamber of the device. The electronic display provided breath-by-breath end-tidal pCO_2 (in mmHg) and f_R (in breaths/min). Data were recorded with time and date of the measurement during the home exercises. In addition, pCO_2 was assessed at the beginning of each treatment session.

Respiration Rate (f_R) was calculated and recorded at the same times as pCO_2.

Spirometric lung function. Lung function was measured with a hand-held electronic spirometer (Jaeger/Toennies, AM2). The best of three expirations was stored in its electronic memory. For the present analysis, we used forced expiratory volume in the first second (FEV_1).

Frequency of asthma symptoms. Frequency of asthma symptoms was assessed during the weekly sessions using a 10-item asthma symptom questionnaire (Steen et al. 1994; abbreviated here as ASQ).

Data Analysis

Weekly home exercise recordings of pCO_2 and f_R were analyzed with a 4×3 two-way repeated measures ANOVA with week (week 1–4) and exercise phase (baseline, paced, unpaced) as within-individual variables.

Table 1 Changes in pCO_2, respiration rate, and asthma outcome variables across training sessions in eight asthma patients undergoing 4 week capnometry- and paced breathing-assisted breathing training

Parameter	Pre-assessment	Post week 1	Post week 2	Post week 3	Post week 4
pCO_2	34.4 (4.3)	34.1 (3.5)	35.9 (5.1)	36.8 (3.5)	38.5 (5.8)
f_R	15.1 (3.9)	13.9 (3.6)	13.4 (3.0)	12.0 (4.2)	10.0 (3.7)
ASQ	1.33 (0.53)	1.00 (0.84)	0.96 (0.70)	0.89 (0.82)	0.75 (0.47)
FEV_1	2.33 (0.47)	2.26 (0.47)	2.24 (0.38)	2.24 (0.36)	2.32 (0.33)

Further one-way repeated measure ANOVAs were calculated for the pCO_2, f_R, and FEV_1 with five levels (initial treatment session and four sessions following the 4 weeks of home exercise) of the within-subject independent variable. Geisser-Greenhouse epsilon correction was applied when indicated. We used polynomial trend analysis to test for linear change over weeks and treatment sessions as opposed to quadratic change, which could result from gains peaking in the first or last weeks of training. Partial eta^2 ($p\eta^2$) was used as a measure of effect size.

Results

Effects of Weekly Home Exercises on pCO_2 and Respiration Rate

PCO_2 showed a steady increase across weeks of home exercises training (effect of Weeks: $F(3,21) = 7.66$, $P < 0.001$, $p\eta^2 = 0.522$). The linear trend was significant, $F(1,7) = 13.19$, $P = 0.008$, but not the quadratic (Fig. 1, upper panel). No significant effect of phase or week by phase was observed. Across weeks, f_R decreased significantly from 12.7 to 10.1 breaths/min for baseline, 12.9 to 6.6 breaths/min for paced conditions, and 12.7 to 7.6 breaths/min for unpaced conditions (effect of week: $F(3,21) = 70.1$, $P < 0.001$, $\varepsilon = 0.55$, $p\eta^2 = 0.909$). The linear trend was significant, $F(1,7) = 132.6$, $P < 0.001$, but not the quadratic (Fig. 1, lower panel). In addition, a significant week by phase interaction, $F(6,42) = 8.74$, $P < 0.001$, $p\eta^2 = 0.555$,was due to slower decline in f_R for baseline than for paced and unpaced feedback conditions, the combination of a linear trend for weeks and a quadratic trend for phase being highly significant, $F(1,7) = 30.08$, $P < 0.001$.

Effects of Treatment on Weekly in-session Measurements

PCO_2 showed a gradual increase across treatment sessions, $F(4,28) = 2.73$, $P < 0.049$, $p\eta^2 = 0.281$, with a significant linear trend, $F(1,7) = 16.86$, $P < 0.005$, but no significant quadratic trend, $F < 1$ (Table 1). Similarly, f_R decreased gradually from 15.1 to 10 min, $F(4,28) = 3.37$, $P < 0.023$,

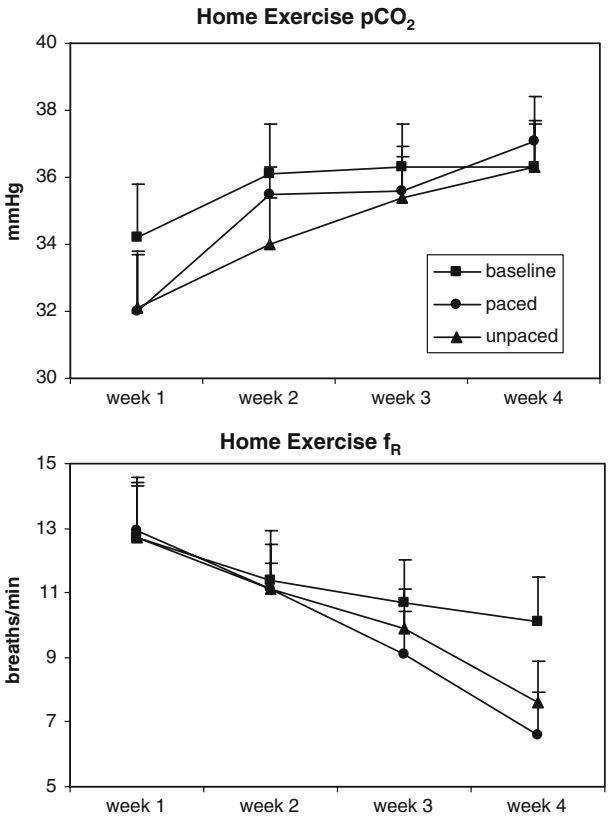

Fig. 1 PCO_2 and respiration rate for 4 weeks of capnometry- and paced breathing-assisted home exercises, with consecutive epochs of *baseline*, capnometry feedback with pacing tones (*paced*), and capnometry feedback without pacing tones (*unpaced*)

$p\eta^2 = 0.325$, with a significant linear trend, $F(1,7) = 7.50$, $P = 0.029$, but no substantial quadratic trend ($F < 1$). Asthma symptoms also gradually declined across weeks of treatment, $F(4,28) = 2.95$, $P = 0.037$, $p\eta^2 = 0.297$, with values decreasing in a linear fashion, $F(1,7) = 11.71$, $P = 0.011$, while the quadratic component was not significant ($F < 1$). No significant change was observed in the FEV_1 ($F < 1$).

Discussion

Our analysis of week-to-week changes in pCO_2 revealed that patients showed steady gains throughout therapy,

practicing with a pacing tape set at 13 breaths/min in the first week and afterwards at increasingly slower rates until reaching the 6-breaths/min pacing tape in the fourth week. These homework gains were present at the beginning of the subsequent training session. Across sessions, basal pCO_2 levels increased by more than 4 mmHg, bringing patients from a hypocapnic into a normocapnic range. In addition, weekly asthma symptoms declined steadily across weeks, which is in line with our earlier analysis that focused on changes from pre- to post-treatment and follow-up (Meuret et al. 2007). Thus, our findings confirm the need for the full 4-week course of pCO_2-biofeedback assisted home exercises to obtain the full benefit of the training. Although we cannot rule out that faster gains would be achieved by initiating lower paced breathing frequencies earlier, this would most likely be perceived as too challenging by most patients. Although not significant in this small sample, an initial drop of pCO_2 was seen during the first week home exercises from baseline phase to paced breathing and feedback phases. In our larger study with panic patients, the same pattern of change was statistically significant (Meuret et al. 2008). One explanation for such a pattern is that patients, when instructed to breathe slower, compensate by breathing deeper, which results in perpetuating or exacerbating hyperventilation (Ley 1991; Meuret et al. 2003).

With respect to asthma symptoms, the gradual decline across weeks also argues against a discrete benefit of slow breathing down to 6 breath/min. Breathing at this rate can have beneficial cardiovascular effects, possibly by entraining the baroreflex (Bernardi et al. 2002; Joseph et al. 2005). Breathing at slow rates like this has been shown to be beneficial in various patient populations (see e.g., Del Pozo et al. 2004; Karavidas et al. 2007). It can also benefit asthma patients with regard to their medication needs and respiratory resistance (Lehrer et al. 1997, 2004) and patients with chronic obstructive pulmonary disease with regard to symptoms and functional status (Giardino et al. 2004). Although the lowest level of symptoms was reached in the fourth week when respiration pacing was set to of 6 breaths/min, the change in symptoms across weeks was not abrupt from week 3 to 4. The closer the breathing training approached the final goal of 6 breaths/min, the lower the reported weekly levels of asthma symptoms. The observed decline in asthma symptoms throughout this paced-breathing based training is also at variance with earlier suggestions that paced breathing may lead to adverse effects in patients with airway obstruction (Sargunaraj et al. 1996).

Although the goal of the paced breathing in the fourth week was 6 breaths/min, many patients never reached this rate. At baseline during the fourth week of home exercises before starting the pacing tones and the pCO_2-feedback, patients f_R was 10.1 breaths/min and the same level was observed in the assessments at the beginning of the final training session. The gap between pacing signal and actual baseline f_R of the patient widened throughout treatment. It is probably unrealistic and undesirable to expect more radical retraining of respiratory timing within this time period, given the trait-like character of breathing patterns (Benchetrit 2000; Myrtek 1984; Shea et al. 1987). Although patients' actual rates increasingly lagged behind the current goal, the decline in rate (probably combined with no compensatory change in tidal volume) was sufficient to elevate pCO_2 into the normocapnic range, which was the main goal of the training.

PCO_2 level baselines of the home exercises were higher for the first week than for the initial training session as well as lower for the fourth week than for the final training session. Because these baseline levels were averaged across all daily exercises, they included a training gain already in the first week as compared to the initial session, as well as a training "deficit" in the fourth week compared with the final session. However, given the demonstrated stable levels of pCO_2 and asthma outcome improvement throughout 2-month follow-up (Meuret et al. 2007), adding further training sessions or home exercise weeks might turn out be an unnecessary burden and expense.

It should be noted that the mechanisms of the observed change in symptoms do not necessarily need to be explained by pCO_2 changes. Although our working model that assumes benefits of pCO_2 increases on asthma pathophysiology is plausible and backed by research in respiratory physiology, we cannot rule out that additional factors may have contributed to the reduction in symptoms. Participants breathing over the weeks came closer to rates that have been shown to be beneficial in studies of respiration rate training in cardiovascular disease (e.g., Schein et al. 2001) and heart rate variability biofeedback studies in general (e.g., Del Pozo et al. 2004; Lehrer et al. 2004). It has been speculated that some of the observed benefits may be related to changes in baroreflex gain, although not all studies could demonstrate such changes. Yet another possibility could be that training to breathe more shallowly could have helped patients avoiding cooling and drying of the airways, commonly thought to be the key mechanism in exercise-induces airway obstruction (McFadden and Gilbert 1994). It could also have helped to avoid bronchoconstriction that can be elicited by deep inhalation, a feature observed with greater asthma severity (Hida et al. 1984; Lutchen et al. 2001). Finally, we must also consider that self-report biases through patients' expectations or social desirability may have been a factor. Due to our lack of a control group we did not guard against such potential influences. However, given the fact that our outcome findings for this training also included a reduction in

within-day variability of lung function (Meuret et al. 2007) as a common indicator of asthma pathophysiology, we can probably exclude that changes observed through our training were limited to patients' experience.

In conclusion, our capnometry-assisted biofeedback training resulted in gradual increases of pCO_2 into the normocapnic range in asthma patients. Our protocol of successively slower paced breathing across four weeks led to steady gains in pCO_2 across a 4-week period, which were accompanied by a gradual decline in asthma symptoms. Future research should further explore mechanisms of the training and determine its efficacy in a larger clinical trial.

References

Benchetrit, G. (2000). Breathing pattern in humans: Diversity and individuality. *Respiration Physiology, 122*, 123–129. doi:10.1016/S0034-5687(00)00154-7.

Bernardi, L., Porta, C., Spicuzza, L., et al. (2002). Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. *Circulation, 105*, 143–145. doi:10.1161/hc0202.103311.

Bruton, A., & Holgate, S. T. (2005). Hypocapnia and asthma: A mechanism for breathing retraining*?*. *Chest, 127*, 1808–1811. doi:10.1378/chest.127.5.1808.

Bruton, A., & Lewith, G. T. (2005). The Buteyko breathing technique for asthma: A review. *Complementary Therapies in Medicine, 13*, 41–46. doi:10.1016/j.ctim.2005.01.003.

Butler, J., Caro, C. G., Alcala, R., et al. (1960). Physiological factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease. *The Journal of Clinical Investigation, 39*, 584–591. doi:10.1172/JCI104071.

Clarke, P. S., & Gibson, J. R. (1980). Asthma hyperventilation and emotion. *Australian Family Physician, 9*, 715–719.

Del Pozo, J. M., Gevirtz, R. N., Scher, B., et al. (2004). Biofeedback treatment increases heart rate variability in patients with known coronary artery disease. *American Heart Journal, 147*, E11. doi:10.1016/j.ahj.2003.08.013.

Fried, R. (1993). *The psychology and physiology of breathing*. New York: Plenum Press.

Giardino, N. D., Chan, L., Borson, S., et al. (2004). Combined heart rate variability and pulse oximetry biofeedback for chronic obstructive pulmonary disease: Preliminary findings. *Applied Psychophysiology and Biofeedback, 29*, 121–133. doi:10.1023/B:APBI.0000026638.64386.89.

Herxheimer, H. (1946). Hyperventilation asthma. *Lancet, 1*, 83–87. doi:10.1016/S0140-6736(46)91225-1.

Hida, W., Arai, M., Shindoh, C., Liu, Y. N., Sasaki, H., & Takishima, T. (1984). Effect of inspiratory flow rate on bronchomotor tone in normal and asthmatic subjects. *Thorax, 39*, 86–92.

Hofmann, S. G., Schultz, S., Meuret, A. E., et al. (2006). Sudden gains during therapy of social phobia. *Journal of Consulting and Clinical Psychology, 74*, 687–697. doi:10.1037/0022-006X.74.4.687.

Hormbrey, J., Jacobi, M. S., Patil, C. P., et al. (1988). CO2 response and pattern of breathing in patients with symptomatic hyperventilation, compared to asthmatic and normal subjects. *The European Respiratory Journal, 1*, 846–851.

Joseph, C. N., Porta, C., Casucci, G., Casiraghi, N., Maffeis, M., Rossi, M., et al. (2005). Slow breathing improves arterial baroreflex sensitivity and decreases blood pressure in essential hypertension. *Hypertension, 46*, 714–718.

Karavidas, M. K., Lehrer, P. M., Vaschillo, E., et al. (2007). Preliminary results of an open label study of heart rate variability biofeedback for treatment of major depression. *Applied Psychophysiology and Biofeedback, 32*, 19–30. doi:10.1007/s10484-006-9029-z.

Lehrer, P., Carr, R. E., Smetankine, A., et al. (1997). Respiratory sinus arrhythmia versus neck/trapezius emg and incentive inspirometry biofeedback for asthma: A pilot study. *Applied Psychophysiology and Biofeedback, 22*, 95–109. doi:10.1023/A:1026224211993.

Lehrer, P. M., Vaschillo, E., Vaschillo, B., et al. (2004). Biofeedback treatment for asthma. *Chest, 126*, 352–361. doi:10.1378/chest.126.2.352.

Ley, R. (1991). The efficacy of breathing retraining and the centrality of hyperventilation in panic disorder: A reinterpretation of experimental findings. *Behaviour Research and Therapy, 29*, 301–304. doi:10.1016/0005-7967(91)90121-I.

Lutchen, K. R., Jensen, A., Atileh, H., et al. (2001). Airway constriction pattern is a central component of asthma severity: The role of deep inspirations. *American Journal of Respiratory and Critical Care Medicine, 164*, 207–215.

McFadden, E. R., Jr, & Gilbert, I. A. (1994). Exercise-induced asthma. *The New England Journal of Medicine, 330*, 1362–1367. doi:10.1056/NEJM199405123301907.

Meuret, A. E., Wilhelm, F. H., & Roth, W. T. (2001). Respiratory biofeedback-assisted therapy in panic disorder. *Behavior Modification, 25*, 584–605. doi:10.1177/0145445501254006.

Meuret, A. E., Wilhelm, F. H., Ritz, T., et al. (2003). Breathing training in panic disorder treatment: Useful intervention or impediment to therapy? *Behavior Modification, 27*, 731–754. doi:10.1177/0145445503256324.

Meuret, A. E., Wilhelm, F. H., & Roth, W. T. (2004). Respiratory feedback for treating panic disorder. *Journal of Clinical Psychology, 60*, 197–207. doi:10.1002/jclp.10245.

Meuret, A. E., Ritz, T., Dahme, B., et al. (2005). Therapeutic use of ambulatory capnometry. In J. S. Gravenstein, M. Jaffe, & D. Paulus (Eds.), *Capnography. Clinical applications*. Cambridge: Cambridge University Press.

Meuret, A. E., Ritz, T., Wilhelm, F. H., Roth, W. T., et al. (2007). Targeting pCO_2 in asthma: Pilot evaluation of a capnometry-assisted breathing training. *Applied Psychophysiology and Biofeedback, 32*, 99–109. doi:10.1007/s10484-007-9036-8.

Meuret, A. E., Wilhelm, F. H., Ritz, T., et al. (2008). Feedback of end-tidal pCO_2 as a therapeutic approach for panic disorder. *Journal of Psychiatric Research, 42*, 560–568. doi:10.1016/j.jpsychires.2007.06.005.

Myrtek, M. (1984). *Constitutional psychophysiology. Research in review*. Orlando, FL: Academic Press.

National Heart Lung and Blood Institute. (1997). *Expert panel report 2: Guidelines for the diagnosis and management of asthma. National asthma education and prevention program*. Washington: U.S Department of Health and Human Services.

O'Cain, C. F., Hensley, M. J., McFadden, E. R., Jr, et al. (1979). Pattern and mechanism of airway response to hypocapnia in normal subjects. *Journal of Applied Physiology, 47*, 8–12.

Osborne, C. A., O'Connor, B. J., Lewis, A., et al. (2000). Hyperventilation and asymptomatic chronic asthma. *Thorax, 55*, 1016–1022. doi:10.1136/thorax.55.12.1016.

Ritz, T., & Roth, W. T. (2003). Behavioral interventions in asthma: Breathing training. *Behavior Modification, 27*, 710–730. doi:10.1177/0145445503256323.

Ritz, T., Kullowatz, A., Bobb, C., et al. (2008a). Psychological triggers and symptoms of hyperventilation in asthma. *Annals of Allergy, Asthma & Immunology, 100*, 426–432.

Ritz, T., Rosenfield, D., Meuret, A. E., et al. (2008b). Hyperventilation symptoms are linked to a lower quality of life in asthma patients. *Annals of Behavioral Medicine, 35*, 97–104.

Sargunaraj, D., Lehrer, P. M., Hochron, S. M., et al. (1996). Cardiac rhythm effects of 125-Hz paced breathing through a resistive load: Implications for paced breathing therapy and the polyvagal theory. *Biofeedback and Self-Regulation, 21*, 131–147. doi:10.1007/BF02284692.

Schein, M. H., Gavish, B., Herz, M., et al. (2001). Treating hypertension with a device that slows and regularises breathing: A randomised, double-blind controlled study. *Journal of Human Hypertension, 15*, 271–278. doi:10.1038/sj.jhh.1001148.

Shea, S. A., Walter, J., Murphy, K., et al. (1987). Evidence for individuality of breathing patterns in resting healthy man. *Respiration Physiology, 68*, 331–344. doi:10.1016/S0034-5687(87)80018-X.

Steen, N., Hutchinson, A., McColl, E., et al. (1994). Development of a symptom based outcome measure for asthma. *BMJ (Clinical Research Ed.), 309*, 1065–1068.

Sterling, G. M. (1968). The mechanism of bronchoconstriction due to hypocapnia in man. *Clinical Science, 34*, 277–285.

Tang, T. Z., & DeRubeis, R. J. (1999). Sudden gains and critical sessions in cognitive behavioral therapy for depression. *Journal of Consulting and Clinical Psychology, 67*, 894–904.

van den Elshout, F. J. J., van Herwaarden, C. L. A., & Folgering, H. T. M. (1991). Effects of hypercapnia and hypocapnia on respiratory resistance in normal and asthmatic subjects. *Thorax, 46*, 28–32.

Wientjes, C. J. (1992). Respiration in psychophysiology: Methods and applications. *Biological Psychology, 34*, 179–203.