Opposing Breathing Therapies for Panic Disorder: A Randomized Controlled Trial of Lowering vs Raising End-Tidal P_{CO_2}

Sunyoung Kim, PhD; Eileen Wollburg, PhD; and Walton T. Roth, MD

ABSTRACT

Background: Teaching anxious clients to stop hyperventilating is a popular therapeutic intervention for panic. However, evidence for the theory behind this approach is tenuous, and this theory is contradicted by an opposing theory of panic, the false-suffocation alarm theory, which can be interpreted to imply that the opposite would be helpful.

Objective: To test these opposing approaches by investigating whether either, both, or neither of the 2 breathing therapies is effective in treating patients with panic disorder.

Method: We randomly assigned 74 consecutive patients with *DSM-IV*–diagnosed panic disorder (mean age at onset = 33.0 years) to 1 of 3 groups in the setting of an academic research clinic. One group was trained to raise its end-tidal P_{CO_2} (partial pressure of carbon dioxide, mm Hg) to counteract hyperventilation by using feedback from a hand-held capnometer, a second group was trained to lower its end-tidal P_{CO_2} in the same way, and a third group received 1 of these treatments after a delay (wait-list). We assessed patients physiologically and psychologically before treatment began and at 1 and 6 months after treatment. The study was conducted from September 2005 through November 2009.

Results: Using the Panic Disorder Severity Scale as a primary outcome measure, we found that both breathing training methods effectively reduced the severity of panic disorder 1 month after treatment and that treatment effects were maintained at 6-month follow-up (effect sizes at 1-month follow-up were 1.34 for the raise-CO_2 group and 1.53 for the lower-CO_2 group; $P < .01$). Physiologic measurements of respiration at follow-up showed that patients had learned to alter their P_{CO_2} levels and respiration rates as they had been taught in therapy.

Conclusions: Clinical improvement must have depended on elements common to both breathing therapies rather than on the effect of the therapies themselves on CO_2 levels. These elements may have been changed beliefs and expectancies, exposure to ominous bodily sensations, and attention to regular and slow breathing.

Trial Registration: ClinicalTrials.gov identifier: NCT00183521

J Clin Psychiatry 2012;73(7):931–939

Submitted: *April 13, 2011; accepted January 27, 2012 (doi:10.4088/JCP.11m07068).*
Corresponding author: *Sunyoung Kim, PhD, Department of Psychology, University of Hawaii, Hilo, HI 96720 (sk47@hawaii.edu).*

Breathing therapy has been widely used as a component of cognitive-behavioral therapy packages for panic disorder[1,2] and sometimes has been the sole component.[3–8] Generally, the rationale for breathing therapy is a hyperventilation theory of anxiety,[9–11] which assumes that hypocapnea caused by hyperventilation is associated with anxiety[12–15] (for a review, see Hardonk and Beumer[14]). To counteract hyperventilation, patients in breathing therapy are instructed to breathe slowly and abdominally, which is expected to increase P_{CO_2} (the partial pressure of carbon dioxide, mm Hg) to normal levels. In a recent study, we showed that a therapy teaching panic disorder patients to raise their P_{CO_2} using capnometer feedback was much more effective than a delayed treatment control.[6] Here we report a study comparing our original treatment to an almost identical therapy that is the theoretical opposite, in that patients are taught to lower rather than to raise their P_{CO_2}. Raising P_{CO_2} has a possible rationale in the false-suffocation alarm theory,[16,17] which postulates that an overly sensitive hypothalamic mechanism produces a feeling of suffocation and panic attacks. This mechanism is triggered by rising P_{CO_2}, to which panic disorder patients are particularly sensitive.

Evidence for and against the 2 respiratory theories has been inconclusive. The following findings support the hyperventilation theory: Voluntary hyperventilation increases anxiety in anxious patients, even triggering panic attacks.[18] Hypocapnea accompanies the panic attacks elicited by CO_2, lactate, bicarbonate, and epinephrine.[19–21] Respiratory stimulants such as doxapram and cholecystokinin can produce panic.[22,23] Hypocapnea has repeatedly emerged as a difference between panic disorder patients and comparison groups during baseline assessment.[12,24–27] However, other studies did not find baseline hypocapnea in panic disorder.[28,29] Even more problematic for hyperventilation theory is the absence of hypocapnea during many naturally occurring panic attacks. In 1 study,[30] 2 of 5 panic attacks were not accompanied by hypocapnea; in another study,[31] 8 of 15; and, in another,[32] 23 of 24. Ley[33] has suggested that perhaps only severe or initial attacks are accompanied by hyperventilation, conceding that the hyperventilation theory of anxiety is limited as an explanation of panic attacks.

Evidence for the false-suffocation alarm theory comes from diverse observations on the fear of suffocation in normal subjects and in panic patients.[16] Perhaps most convincing is the effect of CO_2 inhalation, which precipitates panic attacks in panic disorder patients. Evidence against the false-suffocation alarm theory is the existence of panic disorder patients who do not complain of dyspnea during attacks or who show no respiratory responses. This is compatible with a heterogeneity among panic patients, in that some may fit a respiratory subtype, while others do not.[24,33,34]

Both theories justify respiratory training as a treatment for panic attacks but imply opposite respiratory goals for the training to be effective. If hyperventilation theory is valid, successful prevention of hyperventilation should be necessary and sufficient for eliminating

future attacks, while, if the false-suffocation alarm theory is valid, mild hyperventilation that lowers P_{CO_2} below the lower threshold of the hypersensitive suffocation alarm should prevent attacks. However, evaluating 2 opposing breathing therapies has broader relevance than falsification of 2 theories whose greatest heuristic value may lie in the past. The outcome of these treatments should shed some light on the mechanisms by which respiratory therapies help patients.

In the present study, panic patients were randomly assigned into 1 of 3 groups: raise-CO_2 therapy, lower-CO_2 therapy, or wait-list. The patients in the 2 immediate therapy groups (raise-CO_2 and lower-CO_2) learned to either raise their P_{CO_2} (on the basis of hyperventilation theory) or lower their P_{CO_2} (on the basis of suffocation alarm theory). The 2 therapeutic procedures were closely matched on important nonspecific therapy factor variables such as treatment duration, patient-therapist interaction, direction of attention to bodily sensations (important for controlling interoceptive exposure and distraction), and use of scientific equipment. Such matching allows inferences from the clinical outcomes about the validity of respiratory treatment mechanisms justified by 2 competing theories of panic disorder. The study was registered on ClinicalTrials.gov (identifier: NCT00183521). The Stanford University Institutional Review Board approved and monitored the study.

METHOD

Participants

This study included 74 patients with panic disorder and 30 nonanxious controls. A total of 369 people initially expressed interest in participating and receiving therapy, of which 74 were ultimately allocated to treatment (Figure 1). Panic disorder patients had to have met current *DSM-IV*[35] criteria for diagnosis of panic disorder with or without agoraphobia and accept the possibility of an 8-week treatment delay if assigned to the wait-list. People with a history of schizophrenia; bipolar disorder; dementia; alcohol or drug abuse; current use of medications with pronounced sympathetic, parapsympathetic, or respiratory effects; a current score on the Beck Depression Inventory exceeding 30; or current suicidality were excluded. Controls could not have met current criteria for any psychiatric disorder.

Procedure

Participants, recruited from the general population of the San Francisco Peninsula, received a telephone screening. At the first visit, subjects gave written informed consent and then underwent diagnostic interviews and psychophysiologic assessment. Eligible volunteers were randomly assigned to 1 of 2 immediate treatment groups or to a wait-list. Immediate treatment groups began therapy 1 week after the initial assessment while the wait-list group had to wait 8 weeks. The same psychophysiologic assessment was conducted 1 month after the end of therapy and 8 weeks after the initial assessment for nonanxious controls and wait-list patients so that the interval between testing was the same for all. The 2 immediate treatment groups also received 6-month follow-up assessments.

Clinical Points

- Breathing training designed to alter end-tidal P_{CO_2} (partial pressure of carbon dioxide) using feedback is an efficacious treatment for panic disorder.
- Learning to either raise or lower P_{CO_2} was therapeutic in the current study. Respiratory theories of panic disorder were unable to predict efficacy.
- Possible therapeutic factors common to both therapies are changed beliefs and expectancies, exposure to ominous bodily sensations, and attention to regular and slow breathing.

Treatment

Therapy consisted of 5 weekly sessions of biofeedback-assisted breathing therapy with breathing exercises at home twice daily. Patients were randomly assigned to either hypercapnic (raise-CO_2)[1] or hypocapnic (lower-CO_2)[2] breathing therapy. The therapies were almost identical except for the target P_{CO_2} levels. Therapists were a licensed clinical psychologist and 6 doctoral students in clinical psychology who were supervised by 2 licensed clinical psychologists and a psychiatrist. Each therapist delivered both types of therapy. There were no significant differences in therapy effects and competence ratings between types of therapy and among the therapists.

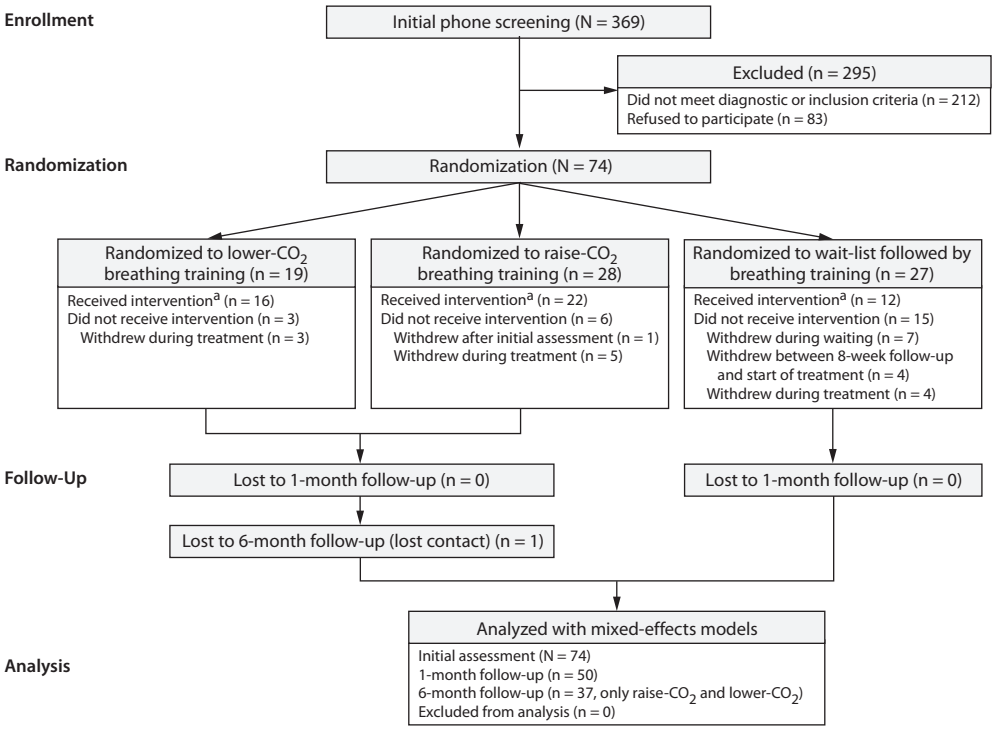
Treatment included education on the physiology of breathing and anxiety, a detailed rationale of the particular treatment, and review of the homework breathing exercises at each session. Patients performed the exercises twice per day using a portable capnometer (Tidal Wave Sp, Model 715; Novametrix Medical System Inc, Clovis, California) with an internal memory that samples exhaled gases drawn by a suction pump from a nasal cannula. The device records end-tidal P_{CO_2}, respiration rate, heart rate, and oxygen saturation. Breathing exercises consisted of 3 parts: a 2-minute baseline, 10 minutes of breathing paced by an audiotape, and 5 more minutes without audio pacing. During the last 2 parts, patients were supposed to breathe more deeply or shallowly to reach the required target P_{CO_2} level of 30 mm Hg (lower-CO_2 group) or 40 mm Hg (raise-CO_2 group) while getting feedback on end-tidal P_{CO_2} and respiration rate from the capnomter display. Patients in both groups were instructed to maintain a respiration rate of 9 breaths per minute throughout.

Psychological Assessment

A multimodal assessment battery consisting of clinician-administered and self-rated measures was given to all participants. On the day of the assessments, participants underwent the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders-Research Version[36] to determine diagnoses. In addition, patients were assessed with the Panic Disorder Severity Scale (PDSS),[37] a clinician-rated instrument that

© Copyright 2012 Physicians Postgraduate Press, Inc.

Figure 1. Study Flowchart



[a]Patients completed all 5 sessions of treatment.
Abbreviation: CO_2 = carbon dioxide.

measures panic disorder severity. Two clinicians administered the PDSS separately for each participant to prevent any possible biases. Interrater reliability was 0.68 at the initial assessment and 0.84 and 0.83 at the 1-month and 6-month follow-up assessments.

Questionnaires included the Anxiety Sensitivity Index,[38] the Beck Depression Inventory,[39] the Mobility Inventory for Agoraphobia,[40] the Agoraphobic Cognitions Questionnaire,[41] the Anxiety Control Questionnaire,[42] the Beck Anxiety Inventory,[43] and the Body Sensations Questionnaire.[41]

Physiologic Assessment

After the diagnostic interviews, the participants were given psychophysiologic tests in our laboratory. In one of the tests, the patient simply sat quietly and breathed normally ("quiet sitting"). At baseline, the quiet-sitting assessment was repeated once. At follow-up, the quiet-sitting assessment was repeated with different instructions: to breathe the way the patient had been taught in therapy (we refer to this version of the test as the "breathing exercise"). During assessment, end-tidal P_{CO_2} was measured continuously with a capnograph, and respiratory chest movement was measured with 2 nonrestrictive elastic belts around the thorax and abdomen. From these data, respiratory variables such as respiration rate (breaths per minute) could be calculated. For a detailed description of the physiologic assessment, recorded channels, and data reduction, see Wollburg et al.[44]

Statistical Analysis

Patients and controls were compared on a number of self-report and physiologic measures using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 16.0 (SPSS Inc, Chicago, Illinois). Statistical significance was set to $P \leq .05$, 2-tailed. Differences in categorical variables were tested with the χ^2 test, while differences in continuous variables were tested with 1-way analyses of variance.

For analysis of the repeated psychological and physiologic data, we followed the recommendations of Bagiella et al[45] and Bryk and Raudenbush.[46] The linear mixed-models approach provides benefits over the traditional repeated-measures analyses of variance—for example, the possibility of modeling missing data by maximum likelihood estimation so that participants with missing data are not excluded. For our data, we assumed unstructured variance covariance structures. Factors were entered as covariates.

Effect sizes were calculated as Cohen d[47] with the equation $d = [\text{Mean}_{\text{GroupA}} - \text{Mean}_{\text{GroupB}}]/\text{SD}_{\text{pooled}}$. The wait-list group was the reference group for comparing initial assessment with 1-month follow-up. Comparison of 1-month and 6-month follow-ups was a measure of the stability of treatment effects. Raise-CO_2 and lower-CO_2 treatments were compared with each other, using the lower-CO_2 group as the reference group.

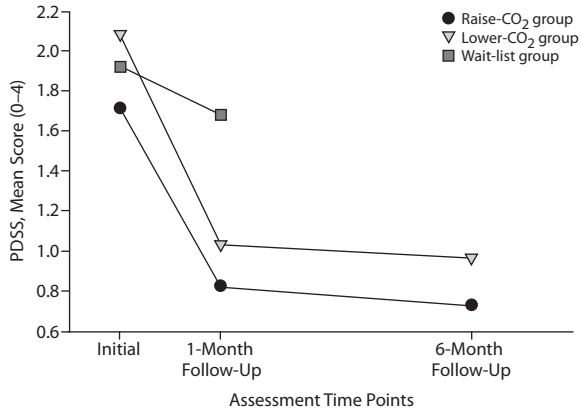
Our primary outcome variable was the PDSS. A number of secondary outcome variables, such as the Anxiety Sensitivity Index, the Beck Anxiety Inventory, and the Beck Depression Inventory, are also of interest, and some of the

Table 1. Demographic and Clinical Characteristics by Group

Characteristic	Nonanxious Controls (n = 30)	Raise-CO_2 Treatment Group (n = 28)	Lower-CO_2 Treatment Group (n = 19)	Wait-List Group (n = 27)	χ^2 or F Ratio[a]	P Value
Women, %	70.0	67.9	68.4	70.4	$\chi^2 = 0.06$	.99
Age, mean (SD), y	43.0 (11.7)	43.8 (10.7)	43.7 (14.5)	38.3 (14.4)	$F = 1.09$	.36
BMI (kg/m^2), mean (SD)	24.2 (4.20)	24.9 (4.08)	26.8 (5.39)	24.7 (3.78)	$F = 1.54$	.21
Ethnicity, non-Hispanic, %	76.7	67.9	42.1	55.6	$\chi^2 = 14.6$	.10
Race, white, %	53.3	60.7	36.8	33.3	$\chi^2 = 16.8$	.53
PDSS score (0–28), mean (SD)	NA	1.80 (0.47)	2.07 (0.65)	1.89 (0.59)	$F = 1.27$	.29
Physiologic measures, mean (SD)						
End-tidal P_{CO_2}, mm Hg	36.8 (3.52)	35.2 (3.63)	37.0 (4.83)	37.0 (4.06)	$F = 1.00$	.40
Respiration rate, breaths/min	11.1 (4.13)	13.1 (3.33)	14.1 (3.78)	11.8 (3.63)	$F = 2.33$	.08

[a]χ^2 from contingency tables; F values from 1-way analyses of variance.
Abbreviations: BMI = body mass index, CO_2 = carbon dioxide, NA = not applicable, P_{CO_2} = partial pressure of carbon dioxide, PDSS = Panic Disorder Severity Scale.

Figure 2. Mean Scores for Panic Disorder Severity Scale (PDSS) at Pretreatment, 1-Month Follow-Up, and 6-Month Follow-Up



Abbreviation: CO_2 = carbon dioxide.

secondary variables in the raise-CO_2 condition appear more therapeutic than in the lower-CO_2 condition. However, in order to avoid the bias of type I errors, we have restricted our statistical hypothesis testing to our preselected primary outcome variable.

RESULTS

Sample Characteristics

Among the panic disorder patients who participated in the study, 56% were white, 19% were Asian or Pacific Islander, 5% were African American, 5% were Native American/Native Alaskan, 12% were of more than 1 race, and 2% declined to report. A total of 54% of the patients were married, 31% had never married, 12% were divorced, 1% were separated, and 1% were widowed. The participants had suffered from panic disorder for a mean of 9.1 years (standard deviation [SD] = 11.6 years) at the time of initial assessment, with a mean age at onset of 33.0 years (SD = 8.9 years).

Baseline Analyses

We used data from 19 patients in the lower-CO_2 group, 28 patients in the raise-CO_2 group, 27 patients in the wait-list group, and 30 nonanxious controls. No significant differences were found in age, sex, race, body mass index (calculated as kg/m^2), baseline P_{CO_2}, or respiration rate (Table 1). The panic disorder patients in the 3 groups did not differ in their initial PDSS scores.

Therapy and Homework Compliance

Therapy session attendance was 100%. Attrition rates were relatively low once the treatment started. Only 3 of 19 participants in the lower-CO_2 group, 5 of 28 in the raise-CO_2 group, and 4 of 27 in the wait-list group dropped out during treatment (see Figure 1). Compliance with home breathing exercises was moderately good (53.3%), considering that the twice-daily homework throughout the treatment period required spending 40–50 minutes every day.

Primary Outcomes

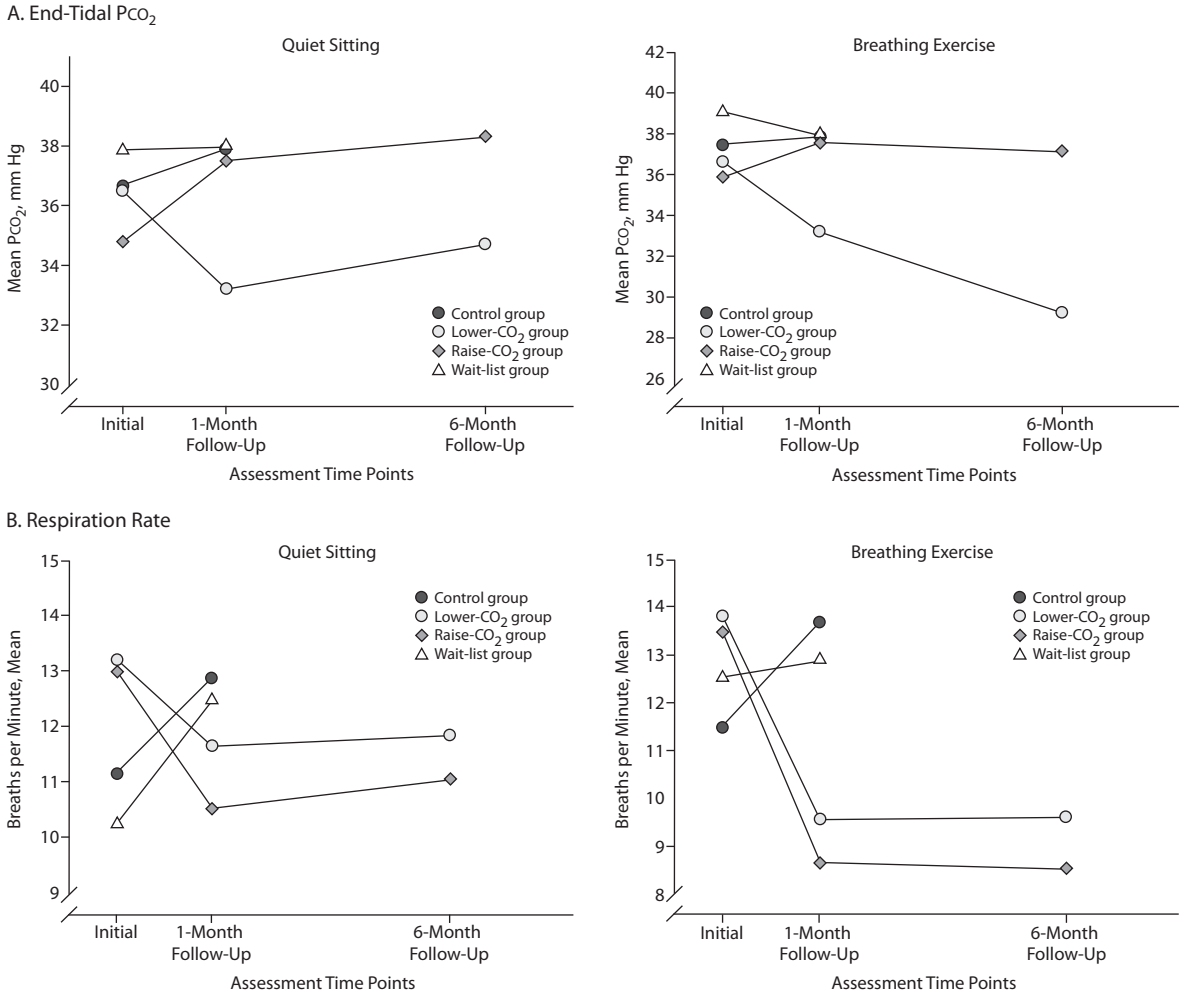
Panic disorder symptom severity. The PDSS was used to measure symptom severity before and after treatment. A linear growth model was applied to PDSS scores over time, resulting in estimated trajectories illustrated in Figure 2. Observed and estimated mean trajectories were very similar.

Panic severity for both the raise-CO_2 and lower-CO_2 groups decreased significantly ($P = .002$) during the 2-month period between initial and 1-month follow-up assessments, both differing significantly from the wait-list group ($P = .001$ for both raise-CO_2 and lower-CO_2 groups) but not from each other. During the same period, panic severity in the wait-list group decreased slightly but not significantly. The effect sizes (Cohen d) for changes between initial assessment and 1-month follow-up were 1.34 for the raise-CO_2 group and 1.53 for the lower-CO_2 group.

Between the 1-month and 6-month follow-ups, data from only the raise-CO_2 and lower-CO_2 groups were available since the wait-list group did not have a 6-month follow-up. The PDSS scores for both groups decreased slightly but not significantly, with no significant difference in slopes. Thus, both groups maintained the decreased PDSS scores at 6-month follow-up.

***End-tidal* P_{CO_2}.** End-tidal P_{CO_2} (CO_2) and respiratory rate were recorded under 2 conditions: normal breathing

Figure 3. Means for (A) End-Tidal P_{CO_2} and (B) Respiration Rate During Quiet Sitting and Breathing Exercise at Pretreatment, 1-Month Follow-Up, and 6-Month Follow-Up



Abbreviations: CO_2 = carbon dioxide, P_{CO_2} = partial pressure of CO_2.

while sitting quietly ("quiet sitting") and, for the treated patients, breathing the way they had been taught in therapy ("breathing exercise"). The longitudinal trend of CO_2 was analyzed with a linear growth model. Figure 3 shows the estimated trajectories of CO_2 based on this model for quiet sitting.

CO_2 in the raise-CO_2 group increased between initial assessment and 1-month follow-up and did not differ significantly from the wait-list group (see Figure 3). In contrast, during the same period, CO_2 in the lower-CO_2 group decreased significantly ($P = .012$), while CO_2 in the wait-list group and the nonanxious control group increased slightly but not significantly. Cohen *d* for CO_2 changes between initial assessment and 1-month follow-up for the raise-CO_2 group was −0.72, and, for the lower-CO_2 group, 0.96. For the interval between the 1-month and 6-month follow-up, there were no statistically significant changes in CO_2 between time points and between groups. During the breathing-exercise assessment, the estimated trajectories of CO_2 for the 4 groups had similar trends to CO_2 for quiet sitting, except that the nonanxious control group insignificantly decreased their CO_2 between initial assessment and 1-month follow-up, while the lower-CO_2 group further decreased its CO_2 significantly ($P = .023$) between the 1-month and 6-month follow-ups (see Figure 3). Cohen *d* for the CO_2 changes between the 1-month and 6-month follow-ups for the raise-CO_2 group was −0.52, and, for the lower-CO_2 group, 0.85.

Respiration rate. During the quiet-sitting assessment, the respiration rate for both the raise-CO_2 and lower-CO_2 groups decreased between initial assessment and 1-month follow-up, differing significantly from the wait-list group ($P = .002$ for the raise-CO_2 group, $P = .040$ for the lower-CO_2 group). During the same period, the respiration rate for both the wait-list group and the nonanxious control group significantly increased ($P = .001$), with no significant difference between them (see Figure 3). Cohen *d* for the respiration rate changes between initial assessment and 1-month follow-up for the raise-CO_2 group was −2.54, and, for the lower-CO_2 group, −2.86. Between 1-month

Table 2. Secondary Outcome Measures at Baseline, 1-Month Follow-Up (follow-up 1), and 6-Month Follow-Up (follow-up 2)

Secondary Outcome Measure	Nonanxious Controls (n = 30), Mean (SD)	Raise CO_2 (n = 28)[a] Mean (SD)	Cohen *d*,[c] Follow-Up 1[d]	Cohen *d*,[c] Follow-Up 2[e]	Lower CO_2 (n = 19)[b] Mean (SD)	Cohen *d*,[c] Follow-Up 1[d]	Wait-List (n = 27), Mean (SD)
Agoraphobic Cognitions Questionnaire (1–5)			1.48	0.23		1.72	
Baseline	1.18 (0.10)	2.20 (0.12)			2.24 (0.15)		2.38 (0.13)
1-Month follow-up	1.15 (0.09)	1.69 (0.10)			1.68 (0.12)		2.04 (0.11)
6-Month follow-up	NA	1.68 (0.14)			1.70 (0.15)		NA
Anxiety Control Questionnaire (0–80)			0.41	−0.38		0.68	
Baseline	139.2 (3.61)	102.6 (4.23)			102.5 (4.88)		101.0 (4.37)
1-Month follow-up	134.4 (3.70)	111.3 (4.34)			109.8 (5.01)		111.5 (4.48)
6-Month follow-up	NA	111.3 (5.06)			107.9 (5.66)		NA
Anxiety Sensitivity Index (0–64)			1.62	0.55		1.83	
Baseline	8.64 (1.96)	26.7 (2.38)			28.1 (2.83)		32.1 (2.62)
1-Month follow-up	7.72 (1.81)	20.1 (2.20)			20.6 (2.62)		29.4 (2.42)
6-Month follow-up	NA	18.9 (2.83)			20.9 (3.23)		NA
Beck Anxiety Inventory (0–63)			0.47	4.29		1.27	
Baseline	2.24 (2.00)	20.9 (2.13)			19.0 (3.11)		19.0 (2.20)
1-Month follow-up	1.71 (2.32)	17.2 (2.47)			12.7 (3.61)		16.4 (2.55)
6-Month follow-up	NA	9.43 (3.00)			19.1 (3.97)		NA
Beck Depression Inventory (0–63)			2.45	0.53		−0.05	
Baseline	2.15 (0.86)	11.4 (1.10)			12.7 (1.46)		11.0 (1.22)
1-Month follow-up	2.08 (0.92)	5.69 (1.17)			10.0 (1.56)		8.23 (1.30)
6-Month follow-up	NA	4.07 (1.37)			9.14 (1.60)		NA
Body Sensations Questionnaire (1–5)			1.03	0.73		5.16	
Baseline	1.20 (0.11)	2.33 (0.14)			2.94 (0.18)		2.57 (0.15)
1-Month follow-up	1.32 (0.13)	2.13 (0.16)			1.98 (0.21)		2.53 (0.17)
6-Month follow-up	NA	1.97 (0.16)			1.95 (0.18)		NA
Mobility Inventory for Agoraphobia, alone (1–5)			1.73	2.50		0.22	
Baseline	1.20 (0.13)	2.11 (0.16)			1.84 (0.19)		2.23 (0.17)
1-Month follow-up	1.84 (0.14)	1.82 (0.16)			1.80 (0.20)		2.23 (0.18)
6-Month follow-up	NA	1.48 (0.15)			1.88 (0.16)		NA
Mobility Inventory for Agoraphobia, accompanied (1–5)			0.87	1.95		−0.08	
Baseline	1.10 (0.10)	1.67 (0.11)			1.58 (0.14)		1.59 (0.12)
1-Month follow-up	1.08 (0.10)	1.53 (0.11)			1.55 (0.14)		1.55 (0.12)
6-Month follow-up	NA	1.31 (0.10)			1.56 (0.12)		NA

[a]Patients with panic disorder treated with hypercapnic (raise-P_{CO_2}) breathing therapy.
[b]Patients with panic disorder treated with hypocapnic (lower-P_{CO_2}) breathing therapy.
[c]Effect size: Cohen $d = [Mean_{GroupA} - Mean_{GroupB}]/SD_{pooled}$.
[d]Initial assessment versus 1-month follow-up, comparing the raise-CO_2/lower-CO_2 groups versus the wait-list group.
[e]1-Month follow-up versus 6-month follow-up, comparing the raise-CO_2 group versus the lower-CO_2 group.
Abbreviations: CO_2 = carbon dioxide, NA = not applicable, P_{CO_2} = partial pressure of carbon dioxide.

and 6-month follow-ups, respiration rate for both groups increased slightly but not significantly, with no significant difference between groups. During the breathing exercise, trends for respiration rate were similar to those for quiet sitting, except that the nonanxious control group significantly increased their respiration rate compared to the wait-list group, whose respiration rate increased insignificantly. Neither the raise-CO_2 nor lower-CO_2 group showed significant respiration rate changes between the 1-month and 6-month follow-ups (see Figure 3). Cohen *d* statistics for the respiration rate changes during this period were −2.33 for the raise-CO_2 group and −2.69 for the lower-CO_2 group.

Secondary Outcomes

Table 2 presents data from the initial assessment and the 1-month and 6-month follow-up assessments for all the secondary outcome measures. Of the secondary measures assessed at the 1-month follow-up, the Agoraphobic Cognitions Questionnaire, the Anxiety Sensitivity Index, and the Body Sensations Questionnaire showed large effect sizes in both the raise-CO_2 and lower-CO_2 groups.

Clinical Significance of Outcome

At the last therapy session's progress evaluation, 91% of the raise-CO_2 group and 100% of the lower-CO_2 group reported that they had experienced a great deal of improvement due to the therapy. One month after treatment, 59.1% of the raise-CO_2 group and 56.3% of the lower-CO_2 group reported having experienced no further panic attacks during the prior 4 weeks. At the 6-month follow-up, 72.7% of the raise-CO_2 group and 60.0% of the lower-CO_2 group were panic-free. Significantly lowered Anxiety Sensitivity Index scores at both follow-up assessments indicated that patients were less afraid of having panic attacks (see Table 2).

Therapist Fidelity Ratings

To ensure that treatment was competently delivered and adhered to the manual, all sessions were audiotaped. Of the 50 treatment completers, the sessions for 20 were randomly selected and rated for therapist competence and adherence. The raters were 4 trained doctoral students not associated with this clinical trial. Overall competence ratings of all therapists ranged from 3 (good) to 5 (excellent), with a mean

rating of 4.05 (SD = 0.76). The mean adherence rating as measured by "application of respiratory behavioral techniques" was 5.35 (SD = 0.67), with rating of 6 being excellent.

DISCUSSION

Both the lower-CO_2 and raise-CO_2 breathing therapies effectively reduced the severity of panic disorder 1 month after treatment, as evidenced by significantly lowered PDSS scores. Effect sizes (treatment compared to wait-list) were large for PDSS: Cohen *d* for the raise-CO_2 group was 1.34, and, for the lower-CO_2 group, 1.53. At 6-month follow-up, treatment effects were maintained in both the raise-CO_2 and lower-CO_2 groups.

Physiologic measurement of respiration showed that treated patients could change their breathing patterns—and did so in the quiet-sitting segment without being explicitly instructed. After treatment, patients in both the raise-CO_2 and lower-CO_2 groups had a significantly lowered respiration rate during both the quiet-sitting and breathing-exercise segments. The goal of both therapy groups was to breathe at 9 breaths per minute. At both follow-up assessments, the lower-CO_2 group showed P_{CO_2} significantly lowered to close to 30 mm Hg, while the raised P_{CO_2} level found in the raise-CO_2 group was not statistically significant. The raise-CO_2 group may have learned how to raise hypocapnic P_{CO_2} levels to 40 mm Hg during anxious, prepanic periods outside the laboratory, but that possibility is testable only by ambulatory measurement. Generally, both patients and controls find that raising P_{CO_2} is harder than lowering it when constrained to breathe at 9 breaths per minute. Lowering P_{CO_2} is achieved relatively easily by breathing more deeply, but raising it above normal is substantially harder unless one is allowed to breathe more slowly.

When designing this study, we assumed that 1 of the 2 breathing therapies would turn out to be superior, vindicating 1 of the 2 opposing respiratory panic theories, but the 2 therapies were equally able to reduce panic symptoms. The therapies were identical, differing only in their rationale and target P_{CO_2} levels. Whether our results have decisively validated or falsified either of the theories that justified the therapies is a thorny issue (for a discussion of falsification, see Roth et al[48]). Suffice it to say that the results of applying the 2 breathing therapies inspired by those theories lead us to wonder what mechanisms, respiratory or otherwise, were at work.

What common factors could have been therapeutic? First, both therapies were able to change beliefs and expectations about the patients' panic attacks. The therapy rationale communicated the ideas that panic symptoms are part of a normal stress response rather than a physiologic collapse, that a cause for panic attacks had been identified scientifically, and that this cause could be controlled by learning to breathe in a certain way. Thus, "catastrophic cognitions," considered by Clark[49] to be the cause of panic attacks, were refuted (evidenced by a drop in Agoraphobic Cognitions Questionnaire scores) without applying the usual cognitive-behavioral therapy procedure of cognitive restructuring. Furthermore, the breathing therapy procedures may have given patients a feeling of control over panic attacks, a way to prevent or abort them, which proved not to be illusory when patients put them to the test as part of home exercise.

Second, in both breathing therapies, patient attention was focused on bodily sensations in general and respiratory sensations in particular and thus must have led to what cognitive-behavioral therapy calls interoceptive exposure. Patients in the raise-CO_2 group could have become desensitized to feelings of suffocation by exposing themselves to higher than their usual CO_2 levels, while the patients in the lower-CO_2 group may have been desensitized to hyperventilation by repeatedly exposing themselves to lower than their usual CO_2 levels. While both groups experienced some discomfort and anxiety during the breathing exercise, the equally low dropout rates from the 2 therapy groups indicate that both breathing therapies were acceptable.

Third, attention to slow and regular breathing at 9 breaths per minute may have had specific relaxing effects that lowered anxiety levels. Attention to breathing is a feature of meditation and yoga practices,[50] although scientific evidence that a particular kind of breathing is able to reduce anxiety is yet to be established. As a relaxation procedure for controlling anxiety, breathing therapy has been suspected of being a "safety aid" that interferes with learning from exposure and achievement of the optimum outcome,[51–53] but empirical support for this theoretical objection is lacking. Even if breathing therapy does teach a safety aid that must be applied each time an attack threatens, the availability, effectiveness, and lack of side effects of this antidote to panic make it at the very least a superior safety aid.

A limitation of our study was that we were unable to recruit many patients with severe panic disorder. Part of this limitation was due to our restrictions on accepting patients with certain medications. In any case, our results might have been different with more severe patients.

Our design had a number of strengths. We tested 4 groups: a nonanxious control group to calibrate the physiologic measures, a wait-list group to compare with the treated groups, and 2 therapy groups to compare to each other. Unlike most psychological treatment outcome studies, we evaluated a single treatment element rather than packages of various elements. Our study assessed patients physiologically in addition to measurement with clinician-administered structured interviews and questionnaires. Instant feedback of CO_2 ensured, for both patients and therapists, that breathing was actually changing in the way it should.

In summary, both of the 2 opposing breathing therapies were beneficial in reducing panic symptoms. Both had moderate to large effect sizes on various psychological measures. The similar low dropout rates for the 2 therapies suggest that the therapies were equally acceptable to patients. Elements common to the therapies, rather than their effect on CO_2 levels, must have been the reason for their success. Possible mechanisms of change include changing beliefs and expectancies (for a review, see Roth[54]), exposure to ominous body sensations, and slowing and regularizing breathing.

Drug names: doxapram (Dopram and others).
Author affiliations: Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California (all authors); Veterans Affairs (VA) Health Care System, Palo Alto, California (all authors); and Department of Differential and Personality Psychology, Dresden University of Technology, Germany (Dr Wollburg). Dr Kim is now affiliated with the Department of Psychology, University of Hawaii, Hilo.
Potential conflicts of interest: None reported.
Funding/support: This research was supported by grants from the National Institutes of Health (RO1 MH-66953) and the Department of Veterans Affairs (ROT-42825).
Previous presentations: Study data were partly presented as an oral presentation at the 29th Annual Conference of the Anxiety Disorders Association of America; March 12–15, 2009; Santa Ana Pueblo, New Mexico; and as a poster session at the 40th Annual Convention of the Association of Behavioral and Cognitive Therapies; November 16–19, 2006; Chicago, Illinois.
Acknowledgments: We give special thanks to William O. Faustman, PhD, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, and Palo Alto VA Health Care System, Palo Alto, California, who supervised and trained our therapists throughout the study period. We also thank the following individuals for their contributions to the study: Jennifer Chen, MS, and Rosalind Lee, MS, PGSP-Stanford PsyD Consortium, Palo Alto University, Palo Alto, California (rated therapy adherence and fidelity); Lindsey Duca, PsyD, Meriter Medical Group, Monona, Wisconsin (provided psychotherapy); Julia Hoffman, PsyD, National Center for Posttraumatic Stress Disorder, Palo Alto VA Health Care System, Palo Alto, California, and National Center for Telehealth and Technology, US Department of Defense, Joint Base Lewis-McChord, Washington (provided psychotherapy); Erin Joyce, PsyD, Harbor-UCLA Medical Center, Torrance, California (provided psychotherapy); Noemi Tesler, Dipl Psych, University Children's Hospital Zurich, Switzerland (rated therapy adherence and fidelity); and Themis A. Yiaslas, PsyD, Northern California VA Health Care System, Martinez, California (provided psychotherapy). These acknowledged individuals have no potential conflicts of interest to report.

REFERENCES

1. Barlow DH, Craske MG, Cerny JA, et al. Behavioral treatment of panic disorder. *Behav Ther*. 1989;20(2):261–282.
2. Telch MJ, Lucas JA, Schmidt NB, et al. Group cognitive-behavioral treatment of panic disorder. *Behav Res Ther*. 1993;31(3):279–287.
3. Clark DM, Salkovskis PM, Chalkley AJ. Respiratory control as a treatment for panic attacks. *J Behav Ther Exp Psychiatry*. 1985;16(1):23–30.
4. Han JN, Stegen K, De Valck C, et al. Influence of breathing therapy on complaints, anxiety and breathing pattern in patients with hyperventilation syndrome and anxiety disorders. *J Psychosom Res*. 1996;41(5):481–493.
5. Hibbert GA, Chan M. Respiratory control: its contribution to the treatment of panic attacks: a controlled study. *Br J Psychiatry*. 1989;154(2):232–236.
6. Meuret AE, Wilhelm FH, Ritz T, et al. Feedback of end-tidal pCO_2 as a therapeutic approach for panic disorder. *J Psychiatr Res*. 2008;42(7): 560–568.
7. Rapee RM. A case of panic disorder treated with breathing retraining. *J Behav Ther Exp Psychiatry*. 1985;16(1):63–65.
8. Salkovskis PM, Jones DR, Clark DM. Respiratory control in the treatment of panic attacks: replication and extension with concurrent measurement of behaviour and pCO_2. *Br J Psychiatry*. 1986;148(5):526–532.
9. Ley R. Agoraphobia, the panic attack and the hyperventilation syndrome. *Behav Res Ther*. 1985;23(1):79–81.
10. Ley R. Blood, breath, and fears: a hyperventilation theory of panic attacks and agoraphobia. *Clin Psychol Rev*. 1985;5(4):271–285.
11. Ley R. Panic disorder: a hyperventilation interpretation. In: Michelson L, Ascher LM, eds. *Anxiety and Stress Disorders: Cognitive-Behavioral Assessment and Treatment*. New York, NY: Guilford Press, 1987: 191–212.
12. Wilhelm FH, Trabert W, Roth WT. Physiologic instability in panic disorder and generalized anxiety disorder. *Biol Psychiatry*. 2001;49(7):596–605.
13. Wilhelm FH, Gerlach AL, Roth WT. Slow recovery from voluntary hyperventilation in panic disorder. *Psychosom Med*. 2001;63(4):638–649.
14. Hardonk JH, Beumer HM. Hyperventilation syndrome. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology*, Vol 38. Amsterdam, The Netherlands: North-Holland Publishing Company, 1979.
15. Ley R. Dyspneic-fear and catastrophic cognitions in hyperventilatory panic attacks. *Behav Res Ther*. 1989;27(5):549–554.
16. Klein DF. False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. *Arch Gen Psychiatry*. 1993;50(4):306–317.
17. Klein DF. Testing the suffocation false alarm theory of panic disorder. *Anxiety*. 1994;1(1):1–7.
18. Maddock RJ, Carter CS. Hyperventilation-induced panic attacks in panic disorder with agoraphobia. *Biol Psychiatry*. 1991;29(9):843–854.
19. Gorman JM, Battista D, Goetz RR, et al. A comparison of sodium bicarbonate and sodium lactate infusion in the induction of panic attacks. *Arch Gen Psychiatry*. 1989;46(2):145–150.
20. Gorman JM, Fyer MR, Goetz R, et al. Ventilatory physiology of patients with panic disorder. *Arch Gen Psychiatry*. 1988;45(1):31–39.
21. van Zijderveld GA, Veltman DJ, van Dyck R, et al. Epinephrine-induced panic attacks and hyperventilation. *J Psychiatr Res*. 1999;33(1):73–78.
22. Abelson JL, Nesse RM. Pentagastrin infusions in patients with panic disorder, 1: symptoms and cardiovascular responses. *Biol Psychiatry*. 1994;36(2):73–83.
23. Abelson JL, Nesse RM, Weg JG, et al. Respiratory psychophysiology and anxiety: cognitive intervention in the doxapram model of panic. *Psychosom Med*. 1996;58(4):302–313.
24. Hegel MT, Ferguson RJ. Psychophysiological assessment of respiratory function in panic disorder: evidence for a hyperventilation subtype. *Psychosom Med*. 1997;59(3):224–230.
25. Munjack DJ, Brown RA, McDowell DE. Existence of hyperventilation in panic disorder with and without agoraphobia, GAD, and normals: implications for a cognitive theory of panic. *J Anxiety Disord*. 1993;7(1):37–48.
26. Papp LA, Martinez JM, Klein DF, et al. Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. *Am J Psychiatry*. 1997;154(11):1557–1565.
27. Roth WT, Wilhelm FH, Trabert W. Voluntary breath holding in panic and generalized anxiety disorders. *Psychosom Med*. 1998;60(6): 671–679.
28. Holt PE, Andrews G. Hyperventilation and anxiety in panic disorder, social phobia, GAD and normal controls. *Behav Res Ther*. 1989;27(4):453–460.
29. Woods SW, Charney DS, Loke J, et al. Carbon dioxide sensitivity in panic anxiety: ventilatory and anxiogenic response to carbon dioxide in healthy subjects and patients with panic anxiety before and after alprazolam treatment. *Arch Gen Psychiatry*. 1986;43(9):900–909.
30. Hibbert GA, Pilsbury D. Hyperventilation in panic attacks: ambulant monitoring of transcutaneous carbon dioxide. *Br J Psychiatry*. 1988;153(1):76–80.
31. Hibbert GA, Pilsbury D. Hyperventilation: is it a cause of panic attacks? *Br J Psychiatry*. 1989;155(6):805–809.
32. Garssen B, Buikhuisen M, van Dyck R. Hyperventilation and panic attacks. *Am J Psychiatry*. 1996;153(4):513–518.
33. Ley R. The many faces of Pan: psychological and physiological differences among three types of panic attacks. *Behav Res Ther*. 1992;30(4):347–357.
34. Biber B, Alkin T. Panic disorder subtypes: differential responses to CO_2 challenge. *Am J Psychiatry*. 1999;156(5):739–744.
35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association, 1994.
36. Spitzer RL, Gibbon M, Skodol AE, et al, eds. *DSM-IV-TR Casebook: A Learning Companion to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Arlington, VA: American Psychiatric Publishing, 2002.
37. Shear MK, Brown TA, Barlow DH, et al. Multicenter collaborative Panic Disorder Severity Scale. *Am J Psychiatry*. 1997;154(11):1571–1575.
38. Peterson RA, Reiss S. *Anxiety Sensitivity Index Manual*. 2nd ed. Worthington, Ohio: International Diagnostic Systems, 1993.
39. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4(6):561–571.
40. Chambless DL, Caputo GC, Jasin SE, et al. The Mobility Inventory for Agoraphobia. *Behav Res Ther*. 1985;23(1):35–44.
41. Chambless DL, Caputo GC, Bright P, et al. Assessment of fear of fear in agoraphobics: the Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire. *J Consult Clin Psychol*. 1984;52(6): 1090–1097.
42. Rapee RM, Craske MG, Brown TA, et al. Measurement of perceived control over anxiety-related events. *Behav Ther*. 1996;27(2):279–293.

43. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56(6):893–897.
44. Wollburg E, Meuret AE, Conrad A, et al. Psychophysiological reactions to two levels of voluntary hyperventilation in panic disorder. *J Anxiety Disord*. 2008;22(5):886–898.
45. Bagiella E, Sloan RP, Heitjan DF. Mixed-effects models in psychophysiology. *Psychophysiology*. 2000;37(1):13–20.
46. Bryk AS, Raudenbush SW. *Hierarchical Linear Models: Applications and Data Analysis Methods. Advanced Qualitative Techniques in the Social Sciences*. Thousand Oaks, CA: Sage Publications, 1992: xvi,265.
47. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
48. Roth WT, Wilhelm FH, Pettit D. Are current theories of panic falsifiable? *Psychol Bull*. 2005;131(2):171–192.
49. Clark DM. A cognitive approach to panic. *Behav Res Ther*. 1986;24(4):461–470.
50. Kabat-Zinn J. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, And Illness*. New York, NY: Delta Trade Paperback/Bantam Dell, 1990.
51. Craske MG, Rowe M, Lewin M, et al. Interoceptive exposure versus breathing retraining within cognitive-behavioural therapy for panic disorder with agoraphobia. *Br J Clin Psychol*. 1997;36(1):85–99.
52. Schmidt NB, Woolaway-Bickel K, Trakowski J, et al. Dismantling cognitive-behavioral treatment for panic disorder: questioning the utility of breathing retraining. *J Consult Clin Psychol*. 2000;68(3):417–424.
53. Garssen B, de Ruiter C, Van Dyck R. Breathing retraining: a rational placebo? *Clin Psychol Rev*. 1992;12(2):141–153.
54. Roth WT. Diversity of effective treatments of panic attacks: what do they have in common? *Depress Anxiety*. 2010;27(1):5–11.