Psychophysiological Effects of Respiratory Challenges before and after Breathing Training in Panic Disorder and Patients suffering from Episodic Anxiety Attacks

DISSERTATIONSSCHRIFT

zur Erlangung des akademischen Grades

Doctor rerum naturalium
(Dr. rer. nat.)

vorgelegt

der Fakultät Mathematik und Naturwissenschaften

der Technischen Universität Dresden

von

Dipl.-Psych. Eileen Wollburg

geboren am 24. Juli 1981 in Frankfurt/Oder

z.Z. Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine & Department of Veterans Affairs (Palo Alto), California, USA

Gutachter: .....
.....
.....

Eingereicht am: .....

Tag der Verteidigung: .....

ACKNOWLEDGEMENTS

I am deeply grateful to my supervisor Dr. Walton T. Roth, MD, for making this experience possible for me and sharing his expertise throughout the entire time. I would also like to thank Prof. Burkhard Brocke, my supervisor at the Technical University of Dresden, for supporting my intention to write my master's thesis at Stanford University and continue on to my dissertation.

All this work would have not been accomplished without the help of many people. Most of all, my co-workers Joo-Young Song, Pearl Chang, and Jen Sauvé with whom I managed many struggles and joys of conducting a research study. They were extremely helpful in all stages of the project. Great thanks to our student therapists Lindsey Duca, Erin Joyce, Themis Yiaslas, Elizabeth Looney, and Julia Hoffman from the Pacific Graduate School of Psychology. Many thanks to all our international students, especially Paola Cojuangco and Julia Wölffel, who helped to a great extent with data preparation, as well as Franziska Bertram, Julia Burau, Ines Behring, Franziska Schreiber, and our volunteer Jane Hsiao.

I cannot express how much I owe to my clinical supervisor Dr. Sunyoung Kim for her encouragement and support in countless ways. My time at Stanford University and the Palo Alto Veterans Hospital would have not been the same without her friendship!

This research was supported by grants to Dr. Roth as principal investigator from the National Institute of Health (RO1 MH-66953) and the Department of Veterans Affairs (ROT-42825).

TABLE OF CONTENTS

ACRONYMS

ANOVA = Analysis of Variance

ASI = Anxiety Sensitivity Index

BDI = Beck Depression Inventory

BH = Breath-holding

BT = Breathing Training

CBT = Cognitive-Behavioral Therapy

CO_2 = Carbon Dioxide

ECG = Electrocardiogram

EDA = Electrodermal Activity

ES = Effect Size

GAD = Generalized Anxiety Disorder

HYPO = Hypoventilation

HR = Heart Rate

HV = Hyperventilation

DSM = Diagnostic and Statistical Manual

MV = Minute Ventilation

NAC = Non-anxious Controls

NSF = Non-specific Fluctuations

OCD = Obsessive-Compulsive Disorder

pCO_2 = Partial Pressure of Arterial Blood Carbon Dioxide

PD = Panic Disorder

RR = Respiration Rate

RRI = Respiratory Rate Instability

RSA_{TF} = Respiratory Sinus Arrhythmia (transfer function)

SCL = Skin Conductance Level

SOP = Social Phobia

VT = Tidal Volume

VTI = Tidal Volume Instability

VHO = Voluntary Hypoventilation Test

VHT = Voluntary Hyperventilation Test

WL = Waiting List

LIST OF TABLES AND FIGURES

SUMMARY

Panic Disorder (PD) has been associated with abnormalities in the respiratory system for a long time, and treatment programs aimed at reversing these abnormalities have been developed. Panicogenic effects of biological challenges have been shown to be altered after successful treatment. Furthermore, there is evidence that anxious non-PD patients show similar responses to these challenges and hence may benefit from some kind of breathing training (BT).

To test these assumptions, we recruited 45 PD patients, 39 Episodic Anxiety (EA) patients who suffered from subclinical panic attacks, and 20 non-anxious controls (NAC). Patients were randomized to one of two versions of a 4-week therapy with BT, either lower or raise end-tidal pCO_2, or a waiting list (WL). Before and after treatment, participants underwent in randomized order a Voluntary Hypoventilation (VHO) test and a Voluntary Hyperventilation (VHT) test in which they were asked to either lower or raise their pCO_2 while psychophysiological measures were recorded. Each test consisted of 3 segments: 1 min baseline, 3 min paced breathing, and 8 min recovery.

Before treatment, PD and EA patients were more anxious, distressed, tense, and worried than NAC, and felt more dizziness, chest pain, and nausea during the laboratory assessment. However, increases in psychological symptoms or physiological sensations from baseline to the paced breathing segments were not different between groups. The two tests produced similar changes except that anxiety and dizziness increased more

during the VHT than VHO. We replicated baseline breathing abnormalities previously reported for PD patients, namely greater respiration rate, tidal volume instability, and number of sighs. However, analyses did not find that patients recovered slower to either challenge. After treatment, both therapies improved on the main outcome measure. Furthermore, BT affected baseline pCO_2, resulting in lower levels in the hypocapnic groups and higher levels in the hypercapnic groups without affecting any other measures.

We conclude that baseline respiratory abnormalities are specific to PD. However, data suggest that the manipulations might have been too weak to elicit other previously reported group differences. Breathing training was equally effective for the lower and raise BT. Hence, factors unrelated to modifying one's pCO_2 must have accounted for the symptomatic improvement. Breathing training should not be restricted to PD but be applied to all patients suffering from anxiety attacks.

ZUSAMMENFASSUNG

Panikstörung (PD) wird seit langer Zeit mit Abnormalitäten im Atmungssystem in Verbindung gebracht. Infolgedessen wurden Therapieprogramme entwickelt, die auf eine Normalisierung der Atmung abzielen. Studien zeigten, dass nach erfolgreichem Therapieabschluss die angstauslösenden Effekte von verschiedenen Atemstresstests vermindert waren. Weiterhin gibt es Hinweise, dass Angstpatienten, die nicht an Panikstörung leiden, ähnliche Reaktionen zeigen und demzufolge von einer Atemtherapie profitieren könnten.

Um diese Annahmen zu überprüfen, wurden 45 Patienten mit Panikstörung, 39 Patienten mit episodischen Angstattacken (EA) und 20 Kontrollpersonen rekrutiert. Patienten wurden in eine von zwei vierwöchigen Atemtherapien randomisiert, in denen die Verminderung oder Erhöhung des endexpiratorischen pCO_2 Niveaus vermittelt wurde, bzw. eine Warteliste. Vor und nach der Therapie wurde bei allen Versuchspersonen ein instruierter Hypoventilations- (VHO) und Hyperventilationstest (VHT) durchgeführt. Die Versuchspersonen wurden gebeten, ihr pCO_2 zu verringern oder zu erhöhen, während verschiedene psychophysiologische Parameter aufgezeichnet wurden. Beide Labortests bestanden aus drei Teilen: 1 Minute Basismessung, 3 Minuten kontrolliertes Atmen, 8 Minuten Erholungsphase.

Vor Beginn der Therapie waren Patienten beider Therapiebedingungen tonisch ängstlicher, gestresster, angespannter und beunruhigter als Kontrollpersonen. Zusätzlich empfanden sie mehr Schwindel, Brustschmerzen und Übelkeit. Allerdings waren die Veränderungen der psychophysiologischen Symptome während der Tests in allen Untersuchungsgruppen gleich. Die Analysen zeigten nur bei PD und nur während der Basismessung Abnormalitäten in der Atmung auf, und zwar höhere Atemfrequenz, Atemvolumeninstabilität, und Anzahl an Seufzern. Eine langsamere Erholung nach Hypo- oder Hyperventilation konnte jedoch nicht repliziert werden. Nach der Therapie zeigten alle PD und EA Patienten signifikante Verbesserung bezüglich des primären Messinstrumentes. Weiterhin wurde das tonische pCO_2 Niveau durch die Therapie in der hypokapnischen Bedingung vermindert und in der hyperkapnischen erhöht.

Wir schlussfolgern, dass Abnormalitäten im Atmungssystem unter Normalbedingungen spezifisch sind für PD. Andererseits waren unsere Labortests wahrscheinlich zu schwach, um die typischen Gruppenunterschiede während Hypo- und Hyperventilation aufzuzeigen. Die Effektivität beider Atemtherapien war vergleichbar. Demzufolge ist die symptomatische Verbesserung Faktoren zuzuschreiben, die nicht mit der direkten Beeinflussung des pCO_2 Niveaus in Verbindung stehen. Die Behandlung mit Atemtherapie sollte nicht auf PD eingeschränkt, sondern auf alle Patienten erweitert werden, die an Angstattacken leiden.

INTRODUCTION

For a long time a link between respiration and emotion has been reported. The respiratory system in anxiety disorders in general, and in Panic Disorder (PD) in particular has come to the attention of researchers. Breathing abnormalities have been postulated as a central feature in the pathophysiology of PD. Evidence comes from studies in which breathing patterns at rest and psychophysiological effects of different biological challenges were investigated. Hyperventilation (HV), inhalation of carbon dioxide (CO_2) gas mixtures, and breath holding, have been used to trigger panic, although their effects on respiration may be opposite, e.g., producing hypocapnia or hypercapnia. The importance of physiology for PD is also reflected in the criteria for panic attacks in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, American Psychiatric Association, 1994). They are a list of some psychological, but mostly physiological symptoms that indicate autonomic and respiratory dysregulation.

Respiratory Abnormalities in Panic Disorder

Baseline Differences

Respiratory measures, particularly end-tidal pCO_2 (partial pressure of CO_2), and cardiac measures have been shown to distinguish between PD and comparison groups at rest. However, evidence for the existence of chronic HV in PD, as indicated by low pCO_2, is mixed. Lower basal pCO_2 levels have been found in several studies to

distinguish healthy volunteers from PD patients (Abelson, Weg, Nesse, & Curtis, 2001; Hegel & Ferguson, 1997; Papp et al., 1997; Roth, Wilhelm, & Trabert, 1998; Salkovskis, Jones, & Clark, 1986; Wilhelm, Trabert, & Roth, 2001; Woods et al., 1986) or from other anxiety disorders such as Generalized Anxiety Disorder (GAD) (Hegel & Ferguson, 1997; Munjack, Brown, & McDowell, 1993; Rapee, 1986; Roth, Wilhelm, & Trabert, 1998). Zandbergen and colleagues (Zandbergen, van Aalst, de Loof, Pols, & Griez, 1993) found lower pCO_2 in PD compared to other anxiety disorders but not to non-anxious controls (NAC). On the other hand, van den Hout et al. (1992) also showed depressed pCO_2 levels in non-PD anxiety disorders. The authors concluded that HV is not specific to PD. In fact, hypocapnia is sometimes absent in PD (de Ruiter, Ruken, Garssen, & Kraaimaat, 1989; Holt & Andrews, 1989a; Kroeze & van den Hout, 1998; Maddock & Carter, 1991; Woods et al., 1986).

Disorganized breathing patterns such as greater tidal volume instability (VTI) (Abelson, Weg, Nesse, & Curtis, 2001; Gorman et al., 1988; Wilhelm, Trabert, & Roth, 2001a, 2001b) or frequent sighing (Abelson, Weg, Nesse, & Curtis, 2001; Wilhelm, Trabert, & Roth, 2001a) have distinguished PD patients from controls in numerous experiments. Greater VTI was even seen during REM sleep (Gorman et al., 1990; Stein, Millar, Larsen, & Kryger, 1995). Gorman et al. (1990) found greater minute ventilation (MV) and tidal volume (VT) in PD compared to Social Phobia (SOP) and NAC. Abelson et al. (Abelson, Nesse, Weg, & Curtis, 1996; Abelson, Weg, Nesse, & Curtis, 2001) replicated this finding of greater MV in PD. Furthermore, they found higher irregularity of respiration rate (RR) in the patients.

Increased breathing frequency is common in PD compared to NAC (Maddock & Carter, 1991), SOP (Holt & Andrews, 1989a), or GAD (Holt & Andrews, 1989a). Rapee et al. (Rapee, Brown, Antony, & Barlow, 1992) observed several anxiety disorders during two respiratory challenges. At baseline, PD with Agoraphobia, OCD, and GAD had higher RR than PD without Agoraphobia or healthy subjects. However, there are examples in which RR, VT, and MV were equal in PD and SOP (Asmundson & Stein, 1994) or NAC (Asmundson & Stein, 1994; Hegel & Ferguson, 1997; Holt & Andrews, 1989a; Papp et al., 1997).

Resting heart rate (HR) has repeatedly been shown to be elevated in PD compared to GAD (Rapee, 1986) or NAC (Bass, Lelliott, & Marks, 1989; Hoehn-Saric, McLeod, Funderburk, & Kowalski, 2004; Roth et al., 1992). Bystritsky et al. (Bystritsky, Craske, Maidenberg, Vapnik, & Shapiro, 2000) divided their patients into panickers and non-panickers in response to a CO_2 challenge and compared them to healthy subjects. Panickers differed in HR and breathing variability from the other groups. On the other hand, some studies recorded equal HRs between patients and controls in the laboratory (Abelson, Nesse, Weg, & Curtis, 1996; Abelson, Weg, Nesse, & Curtis, 2001; Roth, Wilhelm, & Trabert, 1998) or ambulatory (Shear et al., 1992).

Voluntary Hyperventilation

Symptoms of HV and of acute panic often overlap (Bass, Lelliott, & Marks, 1989; Bonn, Readhead, & Timmons, 1984; Cowley & Roy-Byrne, 1987; Gorman et al., 1984; Hibbert & Pilsbury, 1988; Maddock & Carter, 1991; Rapee, 1986). Some studies, though,

failed to show a link between hypocapnia and naturally occurring panic attacks (Garssen, Buikhuisen, & van Dyck, 1996; Hibbert & Pilsbury, 1988, 1989). Nevertheless, voluntary HV has widely been used as a respiratory agent to provoke panic in PD, and has repeatedly evoked a stronger psychophysiological response than in comparison groups. An increase in anxiety and panic symptoms is typical during HV, but usually with greater increases in PD than NAC (Gorman et al., 1984; Holt & Andrews, 1989a, 1989b; Maddock & Carter, 1991; Nardi, Valenca, Nascimento, & Zin, 2002b; Wilhelm, Gerlach, & Roth,, 2001). The same is the case for other anxiety disorders (Nardi, Valenca, Nascimento, & Zin, 2002b; Rapee, 1986; Wilhelm, Gerlach, & Roth, 2001) or even depression (Nardi, Valenca, Nascimento, & Zin, 2001). In Bass et al.'s (Bass, Lelliott, & Marks, 1989) study, only patients who reported that symptoms produced by HV were similar to their usual panic, had more somatic symptoms during recovery than controls. A number of studies have shown that HV elicits more panic attacks in PD than NAC (Maddock & Carter, 1991; Martinez et al., 1998; Nardi, Valenca, Nascimento, & Zin, 2001, 2002b; Nardi et al., 2006; Papp et al., 1997). However, in a study by Gorman et al. (1994), numbers of panic attacks were only different between groups according to the patients' self-report, not according to the judgment of an outside assessor. Another study applied a HV challenge to healthy volunteers and various anxiety disorder patients (Holt & Andrews, 1989a). The authors found that panic patients had smaller VTs than NAC during HV, which they interpreted as a restriction of breathing depth due to fear of the consequences of the provocation.

A common phenomenon in PD is slower psychophysiological recovery from HV. Wilhelm et al. (Wilhelm, Gerlach, & Roth, 2001) investigated PD, SOP, and NAC during several periods of brief HV. They found greater anxiety in PD and SOP compared to controls at baseline, HV, and recovery. PD patients exhibited more panic attacks during recovery but were equal to SOP during HV itself. Moreover, PD showed slower recovery of pCO_2, HR, and skin conductance level (SCL), and higher scores on most self-reported respiratory items than the two other groups. Ball and Shekkar (1997) found more dizziness in PD during recovery from 30 seconds of overbreathing compared to NAC. Patients also exhibited greater baseline dizziness, but the differences during recovery were not accounted for by them. Gorman and colleagues (1988) divided their patients into panickers and non-panickers. The first group had lower pCO_2 levels during HV recovery than non-panickers and controls. The same pattern was seen in another study: panicking patients showed slower pCO_2 recovery and a greater increase in RR compared to baseline (Maddock & Carter, 1991). Friedman et al. (Friedman, Mathis, Hayes, Renshaw, & Dager, 2006) also observed slower recovery of pCO_2 in PD.

However, some studies have failed to find more panic attacks in PD during HV (Bass, Lelliott, & Marks, 1989; Gorman et al., 1988; Griez & Schruers, 1998; Zandbergen, Lousberg, Pols, de Loof, & Griez, 1990) or could only show a difference in self-report but not physiological measures. In a recent study from our laboratory (Wollburg, Roth, Conrad, Meuret, & Kim, in press) we investigated PD patients and healthy volunteers during two levels of HV and did not find the differences in the physiological measures reported in previous experiments (see above). Rapee (1986)

compared PD and GAD patients on their reaction to brief HV and found no differences in change values of pCO_2 or VT from baseline to recovery. Moreover, similar increases in HR during HV were seen in both groups. However, PD patients experienced more symptoms during HV and rated them as more intense. In a later experiment (Rapee, Brown, Antony, & Barlow, 1992), the PD group showed a greater response than other anxiety disorders or NAC. PD patients exhibited more fear, anxiety, and physical and other cognitive symptoms of anxiety, and rated them as more intense. A study conducted by Asmundson & Stein (1994) with PD and SOP patients found no group differences in any of the physiological measures recorded, but both patient groups exhibited more panic attacks and a higher global symptom severity score than NAC. Whittal & Goetsch (1995) applied a 2 minute HV challenge to PD patients, infrequent panickers, and panic-free subjects with either low or high anxiety (based on the State-Trait Inventory). They found no group differences in physiological measures but in sensations and cognitions. Panic-free, low anxiety subjects endorsed less intense sensations and anxious cognitions than the other three groups. PD patients and infrequent panickers exhibited more intense cognitions during HV than the other two groups.

Voluntary Hypoventilation

Underbreathing as well as overbreathing can cause panic responses. Hypoventilation (HYPO) induced by inhalation of CO_2-enriched gas mixtures is one of the most widely studied laboratory markers of PD. Subjects inhale CO_2-enriched air of varying concentrations for a prolonged time, or take single- or double-vital capacity breaths of such air. Although less frequently used, hypercapnia (high CO_2 level) can also

be produced by breath-holding (BH) (Asmundson & Stein, 1994; Rassovsky, Abrams, & Kushner, 2006; Roth, Wilhelm, & Trabert, 1998). Typically the breath is held as long as possible by the subject, or subjects rebreathe their own exhaled CO_2 (Katzman et al., 2002; Papp, Martinez, Klein, Coplan, & Gorman, 1995). A general criticism of these methods is that CO_2 concentrations are usually higher than those occurring naturally. Too high concentrations may obliterate differences between experimental and control groups (Papp, Klein, Martinez et al., 1993; Papp et al., 1997). For instance, Gorman et al. (1988) showed that with 5% CO_2, PD groups experienced more panic attacks than other anxiety disorders or NAC, but the differences between the patient groups disappeared with 7% CO_2. Nevertheless, inhaling CO_2 appears to be a very reliable panicogenic agent. Comparison studies of HV and HYPO often yielded the result that the latter is a more potent anxiogenic stimulus (Gorman et al., 1984, 1988, 1994; Papp et al., 1997; Zandbergen, Lousberg, Pols, de Loof, & Griez, 1990).

In numerous experiments, an exaggerated response to CO_2 inhalation has been observed in PD compared to healthy controls (Bystritsky & Shapiro, 1992; Gorman et al., 1984, 1994; Griez, de Loof, Pols, Zandbergen, & Lousberg, 1990; Kent et al., 2001; Papp, Klein, Martinez et al., 1993; Papp et al., 1997; Schmidt, Forsyth, Santiago, & Trakowski, 2002; Rassovsky, Abrams, & Kushner, 2006; van den Hout, Marcel A., van der Molen, Griez, Lousberg, & Nansen, 1987; Woods, Charney, Goodman, & Heninger, 1988), other anxiety disorders (Griez, de Loof, Pols, Zandbergen, & Lousberg, 1990; Nardi et al., 2003; Papp, Klein, Martinez et al., 1993; Perna, Gabriele, Caldirola, & Bellodi, 1995), and depression (Kent et al., 2001). Schmidt et al. (Schmidt, Forsyth,

Santiago, & Trakowski, 2002) found a greater response to CO_2 in both self-report and physiology. They subtyped their PD patients and NAC based on subjective distress and autonomic arousal during 35% CO_2 inhalation and found that the majority could be classified as either prototypic panic (presence of subjective distress and arousal) or cognitive panic (presence of subjective distress, but only minimal arousal).

Gorman and colleagues (2001) observed lower resting pCO_2 levels in PD patients who subsequently panicked to 5% CO_2 inhalation than in non-panicking PD. Compared to depression, premenstrual dysphoric disorder, and non-anxious controls, panic attacks were triggered more often in patients with PD and premenstrual dysphoric disorder. The stronger reaction to CO_2 was due to an occurrence of a panic attack, but not associated with the diagnostic group which led to the conclusion that the panic reaction involves a generalized fear response and can therefore occur in subjects without a diagnosis of PD. Similar results were obtained by Kent et al. (2001). Verburg and colleagues (Verburg, Griez, Meijer, & Pols, 1995) observed that PD patients had a greater increase in anxiety to 35% CO_2 than did GAD patients, but that total panic symptom scores rose equivalently. The authors concluded that an increase in anxiety in reaction to CO_2 inhalation is specific to PD, but not an increase in panic symptoms. Some researchers have speculated that certain subgroups of non-PD anxiety disorders are prone to the same false suffocation alarms as PD (Caldirola, Perna, Arancio, Bertani, & Bellodi, 1997; Perna, Gabriele, Caldirola, & Bellodi, 1995). One repeatedly observed sign of an exaggerated response to CO_2 in PD is premature termination of CO_2 inhalation (Gorman et al., 1994; Papp et al., 1997; Rassovsky, Abrams, & Kushner, 2006) or premature

termination of BH (Asmundson & Stein, 1994). However, some HYPO studies have only found effects in the self-report domain when PD was compared to other anxiety disorders (Asmundson & Stein, 1994; Rapee, Brown, Antony, & Barlow, 1992; Verburg, Griez, Meijer, & Pols, 1995) or NAC (Lynch, Bakal, Whitelaw, Fung, & Rose, 1992; Rapee, Brown, Antony, & Barlow, 1992; Woods, Charney, Goodman, & Heninger, 1988). Other studies did not find any CO_2 hypersensitivity in PD compared to NAC (Gorman et al., 1990; Katzman et al., 2002; Roth et al., 1992; Roth, Wilhelm, & Trabert, 1998) or other anxiety disorders (Antony, Brown, & Barlow, 1997; Caldirola, Perna, Arancio, Bertani, & Bellodi, 1997; Gorman et al., 1990; Roth, Wilhelm, & Trabert, 1998).

In summary, respiratory abnormalities at baseline and in response to over- or underbreathing, have often appeared specific for PD (Griez, de Loof, Pols, Zandbergen, & Lousberg, 1990; Nardi, Valenca, Nascimento, & Zin, 2002b; Nardi et al., 2003; Papp, Klein, Martinez et al., 1993; Perna, Gabriele, Caldirola, & Bellodi, 1995; Rapee, 1986; Wilhelm, Gerlach, & Roth, 2001). On the other hand, some studies indicated that a greater reaction to voluntary HV and CO_2 inhalation is not necessarily specific to PD. In several studies, equal responses were observed in PD and non-PD anxiety disorders (Antony, Brown, & Barlow, 1997; Asmundson & Stein, 1994; Caldirola, Perna, Arancio, Bertani, & Bellodi, 1997; de Ruiter, Ruken, Garssen, & Kraaimaat, 1989; Gorman et al., 1990; Rapee, Brown, Antony, & Barlow, 1992) or NAC (Antony, Brown, & Barlow, 1997 Asmundson & Stein, 1994; Bass, Lelliott, & Marks, 1989; Carter, Suchday, &

Gore, 2001; Caldirola, Perna, Arancio, Bertani, & Bellodi, 1997; Ehlers et al., 1986; Griez & Schruers, 1998; Gorman et al., 1988, Gorman et al., 1990; Holt & Andrews, 1989b).

How can these inconsistencies be explained? The possibility of subtypes of panic that are associated with different reactions to biological challenges has been raised by several researchers (Biber & Alkin, 1999; Hegel & Ferguson, 1997; Ley, 1992). A common distinction among panic patients has been posited, namely, differentiating between "respiratory" and "non-respiratory" subtypes based on symptoms during usual attacks. Research has shown that the first subtype has a higher sensitivity to biological challenges than the latter (Abrams, Rassovsky, & Kushner, 2006; Biber & Alkin, 1999; Nardi et al., 2006; Valença, Nardi, Nascimento, Zin, & Versiani, 2002). Typically, the definition introduced by Briggs et al. (Briggs, Stretch, & Brandon, 1993) has been used. On the basis of cluster analysis and principal component analysis, Briggs et al. (Briggs, Stretch, & Brandon, 1993) found a subgroup with prominent respiratory symptoms defined as the presence of at least 4 of the following symptoms: shortness of breath, choking/smothering sensations, chest pain/discomfort, tingling/numbness, or fear of dying. The residual group endorsed fewer than 4 of those. It is obvious that a cognitive symptom (fear of dying) was part of the respiratory subtype but dizziness, a clear HV symptom, was not included. In a recent study (Meuret et al., 2006), a three-factor solution for symptom dimensions from intensity ratings of the DSM-IV panic attack symptoms was found: cardio-respiratory, autonomic/somatic, and cognitive subtypes of panic attacks. This study confirmed the very early results by Cox et al. (1994). Another

classification by Schmidt et al. (Schmidt, Forsyth, Santiago, & Trakowski, 2002) was based on subjective distress and autonomic arousal in response to CO_2 inhalation. They distinguished between prototypic (high subjective distress, high arousal), cognitive (high subjective distress, low arousal), and nonfearful (low subjective distress, high arousal) attacks. The first two were dominantly found in PD in response to the challenge. Finally, a distinction made by early studies was between panickers and non-panickers in response to HV or CO_2 inhalation (Gorman et al., 1988; Maddock & Carter, 1991).

Physiological Theories of Panic Disorder

Currently, there are two prominent respiratory theories of PD, both of which postulate a role for HV: Ley's Hyperventilation Theory and Klein's Suffocation False Alarm Theory. One views HV as the cause and one as the consequence of panic. Ley's model (1985) proposes that panic attacks are caused by HV and the misinterpretation of its symptoms. Later he added a vicious circle mechanism, a lowered threshold for panic due to chronic HV, and an emphasis on the automatic fear-eliciting nature of involuntary dyspnea (Ley, 1987, 1989). If the state of hypocapnia (low pCO_2) persists and dyspnea is perceived as incontrollable and life-threatening, a panic attack will occur. At some point in the learning history of the patient, HV and accompanying symptoms led to anxiety which intensified HV and accompanying symptoms, creating a vicious circle ending in panic. A further elaboration of the theory focused on the distinction between different kinds of panic attacks - respiratory, cognitive, and anticipatory – characterized by

different psychological and physiological symptoms (Ley, 1992). Evidence for the hyperventilation theory comes from studies that observed lower basal pCO_2 in PD (Hegel & Ferguson, 1997; Papp et al., 1997; Rapee, 1986; Roth, Wilhelm, & Trabert, 1998; Salkovskis, Jones, & Clark, 1986), a co-occurence of hypocapnia and panic attacks (Gorman et al., 1988; Griez & van den Hout, 1987; Salkovskis, Warwick, Clark, & Wessels, 1986), a stronger psychological response to voluntary HV (Antony, Brown, & Barlow, 1997; Gorman et al., 1994; Holt & Andrews, 1989a), or a slower recovery from HV (Gorman et al., 1988; Maddock & Carter, 1991; Wilhelm, Gerlach, & Roth,, 2001). However, as noted above, hypocapnia is not always present in PD at baseline (Holt & Andrews, 1989a, Woods et al., 1986) or during panic attacks (Garssen, Buikhuisen, & van Dyck, 1996; Hibbert & Pilsbury, 1988). Ley suggested that possibly only initial or severe panic attacks are accompanied by hypocapnia. Other contrary findings include observations of hypocapnia in anxiety disorders other than PD (van den Hout et al., 1992) and the fact that hypercapnea appears to be a better panicogenic agent than HV (Gorman et al., 1984, 1994; Papp et al., 1997; Rapee, Brown, Antony, & Barlow, 1992)

The basic tenet of the Suffocation False Alarm Theory is that hypercapnia, or less often hypoxia, causes panic (Klein, 1994). According to Klein, PD patients are particularly sensitive to hypercapnia but may react secondarily to suffocation feelings with HV or frequent sighing. He assumes a faulty, overly sensitive physiological mechanism, a suffocation alarm monitor that is triggered when the oxygen supply is not actually being compromised, falsely signalling hypoxia (Klein, 1993). As a result, patients experience a feeling of suffocation or dyspnea that causes sudden respiratory

distress and panic. Furthermore, Klein states that the set point for the alarm may be lower in PD or just spontaneously fires. Therefore, patients may hyperventilate to create a buffer zone and keep the CO_2 level below the threshold that would trigger a false alarm by incidental fluctuations. Opposite from Ley, chronic HV in PD is seen as an adaptive, compensative mechanism rather than a cause of panic. Klein describes three types of panic associated with different psychological and physiological symptoms (Klein & Klein, 1989): spontaneous panic, stimulus-bound panic, and situationally predisposed panic.

A number of findings support this model, for instance, studies that showed an exaggerated response of PD patients to CO_2 inhalation (Gorman et al., 1994, 2001; Nardi et al., 2003; Rapee, Brown, Antony, & Barlow, 1992), premature termination of CO_2 inhalation (Papp et al., 1997) or of BH (Asmundson & Stein, 1994) as an attempt to avoid activating the suffocation monitor, greater chemoreceptor sensitivity (Lousberg, Griez, & van den Hout, 1988), and greater responses to provocations such as breath holding (Asmundson & Stein, 1994; Rassovsky, Abrams, & Kushner, 2006) and lactate infusions (Gorman et al., 1988; Sloan et al., 1999). Lactate is a signal to the suffocation alarm monitor that causes central chemoreceptors to misinterpret fluctuations in pH as life-threatening hypoxia. Slower recovery from HV can be interpreted by this model as a reluctance of patients to let their CO_2 rise. However, not all studies have found PD-specific hypersensitivities to hypercapnia or a lower threshold (Antony, Brown, & Barlow, 1997; Caldirola, Perna, Arancio, Bertani, & Bellodi, 1997; Gorman et al., 1990; Katzman et al., 2002; Roth, Wilhelm, & Trabert, 1998; Schmidt, Telch, & Jaimez, 1996).

Treatment of Breathing Abnormalities

The panicogenic effects of breathing challenges can be altered by successful treatment of PD (Gorman, Martinez, Coplan, Kent, & Kleber, 2004; Martinez et al., 2001; Meuret, Wilhelm, Ritz & Roth, in press; Salkovskis, Jones, & Clark, 1986; Schmidt, Lerew, & Jackson, 1997; Sullivan et al., 2004; Valença, Nardi, Nascimento, Zin, & Versiani, 2002a). Since respiratory abnormalities have been found for decades to be present in PD, treatment programs have been developed that are aimed at modifying pathogenic breathing. They are usually based on a HV model and hence aimed at reversing hypocapnia and reducing dysfunctional respiration by teaching slow, abdominal breathing with the help of audiotapes, simple breath counting, or capnographic feedback (Meuret, Wilhelm, & Roth, 2001; Meuret, Wilhelm, Ritz & Roth, 2003). Additionally, patients learn to reinterpret their physical symptoms as part of a normal bodily reaction, the fight-flight response. Several studies have applied variations of BT alone to PD patients (Clark, Salkovskis, & Chalkley, 1985; Hibbert & Chan, 1989; Salkovskis, Jones, & Clark, 1986) or as one component of a treatment package (Bonn, Readhead, & Timmons, 1984; Craske, Rowe, Lewin, & Noriega-Dimitri, 1997; Schmidt et al., 2000), and have shown therapeutic benefits. However, not all studies found BT to be efficacious; as part of treatment packages it has produced mixed results. For instance, Craske et al. (Craske, Rowe, Lewin, & Noriega-Dimitri, 1997) and Schmidt et al. (2000) did not find an additive effect of BT following CBT. Some researchers assume that only PD patients who recognize a similarity between the symptoms produced by HV and those usually experienced during their panic attacks benefit from BT. Bonn et al. (Bonn,

Readhead, & Timmons, 1984), for example, only offered BT to those patients who responded to a HV challenge. Even cognitive approaches (Clark, 1986) ascribe a role to HV, albeit a secondary one. CBT focuses on the maladaptive interpretation of symptoms that causes PD patients to hyperventilate and become anxious. Skills for combating HV may be used as a safety-aid and therefore counteract the rationale of CBT (Craske, Rowe, Lewin, & Noriega-Dimitri, 1997; Schmidt et al., 2000). Proponents of BT on the other hand argue that this approach could lead to a false assumption that HV is normal and does not need treatment.

Studies giving BT to patients with anxiety disorders seldom record physiological measures (see Wollburg, Kim, Conrad, & Roth, 2007). This is a flaw since physiological processes are the main target of the treatment. Few studies used respiratory measures as part of the outcome evaluation. Salkovskis et al. (Salkovskis, Jones, & Clark, 1986) found a lower resting pCO_2 in patients with panic attacks than in controls, which normalized with treatment by paced breathing. A study carried out by Bonn and colleagues (Bonn, Readhead, & Timmons, 1984) showed that diaphragmatic breathing in combination with exposure in agoraphobics was superior at the 6-months follow up assessment in terms of RR and some clinical measures, for instance, the elimination of panic attacks. Our laboratory has developed a respiratory biofeedback-assisted therapy for PD in which people are trained to raise their end-tidal pCO_2 by slow, diaphragmatic breathing (Meuret, Wilhelm, & Roth, 2001; Meuret, Wilhelm, Ritz, & Roth, in press). Results also showed a lower basal pCO_2 before treatment and an increase to normal levels after BT along with improvement on clinical measures. In the current study we

expanded this treatment. PD patients were randomly assigned to two different therapy groups that teach either anti-hyperventilatory breathing or lowering of end-tidal pCO_2. The first therapy is in line with Ley's theory, the latter with Klein's.

Respiratory Abnormalities in other Anxiety Patients

Respiratory abnormalities have been shown to be present in anxiety disorders other than PD. Wilhelm et al. (Wilhelm, Trabert, & Roth, 2001a, 2001b) observed lower basal pCO_2 and increased VTI and sighing in both PD and GAD. Driving phobia patients without PD showed significant hypocapnia and increased respiratory variability while driving (Alpers, Wilhelm, & Roth, 2005). Furthermore, hypersensitivity to respiratory challenges has also been found in phenomenologically related conditions, including limited symptom episodes (Schmidt, Lerew, & Jackson, 1997). CO_2 inhalation provokes a panic response in patients without PD, even if milder than in PD (Gorman et al., 1990; Gorman et al., 2001; Papp, Klein, Martinez et al., 1993; Perna et al., 1994; Perna, Gabriele, Caldirola, & Bellodi, 1995; Rapee, Brown, Antony, & Barlow, 1992). Caldirola et al. (Caldirola, Perna, Arancio, Bertani, & Bellodi, 1997) found the same increase in anxiety in PD and SOP in response to CO_2 inhalation; Nardi et al. (Nardi et al., 2003) showed that PD did not differ in the increase in anxiety to SOP and GAD in reaction to BH. These findings indicate that similar false suffocation alarm monitors to the ones postulated for PD may also be present in other anxiety disorders or subgroups of them. Perna et al. (Perna et al., 1994; Perna, Gabriele, Caldirola, & Bellodi, 1995) have

shown that clinical severity of PD is unrelated to the vulnerability to CO_2 inhalation. They conclude that regardless of the diagnostic group, the experience of panic attacks during CO_2 inhalation rather than meeting the full criteria for PD accounted for the exaggerated response. Furthermore, respiratory control has been successfully applied in patients with panic attacks (e.g., Salkovskis, Jones, & Clark, 1986; van den Hout, Marcel A., van der Molen, Griez, Lousberg, & Nansen, 1987). In addition, many patients suffer from anxiety attacks that do not meet full DSM criteria for panic attacks. In a study by de Beurs et al. (1994) only 60% of the recorded attacks fulfilled DSM criteria of at least four symptoms. About 20% of the panic attacks involved only one severe symptom or only mild symptoms, and about the same percentage of episodes lasted longer than an hour. The authors conclude that major attacks are predominantly long-lasting and that just one symptom, if intense enough, can lead to the subjective judgment of a panic attack. Margraf et al. (Margraf, Taylor, Ehlers, Roth, & Agras, 1987) found that the average panic attack in their sample lasted about a half hour and concluded that "any cutoff above two symptoms is arbitrary". These results give rise to the question of how people with anxiety attacks with only two accompanying DSM-IV panic attack symptoms would react to respiratory challenges.

The primary goal of the study reported here was to investigate whether treatment with one of two kinds of breathing retraining (hypocapnic vs. hypercapnic breathing) would attenuate the psychophysiological reactions of PD patients to hypoventilation and hyperventilation. In accordance with the majority of recent psychophysiological findings, we hypothesized that PD would have a stronger psychophysiological reaction than NAC

to both respiratory challenges. After treatment, both treatment conditions would show less psychological and physiological distress to the challenges since the therapy targeted normalization of respiration. Patients in the hypercapnic condition would have higher, and patients in the hypocapnic lower resting pCO_2 levels. Hence, we expected that patients in the first condition would reach higher pCO_2 levels at the end of HYPO and recovery faster from HV at post-treatment than patients who received the hypocapnic treatment. The two groups would not differ in their ability to hyperventilate since HV is a procedure that is easier to carry out than HYPO. In addition to PD patients, the study reported below investigated a second patient population suffering from subclinical panic attacks, which we termed Episodic Anxiety (EA) patients. Since they show a clinical overlap with PD, there is reason to assume similar but possibly milder reactions to respiratory challenges, and a benefit from breathing training. We hypothesized that the EA patients would show a similar but milder response than panic patients to the respiratory challenges, which would be further attenuated by treatment.

METHOD

Inclusion Criteria

This study compared Panic Disorder and Episodic Anxiety patients with non-anxious controls. Participants were recruited from the general population of the Peninsula and San Francisco South Bay region. PD patients must have met current DSM-IV diagnosis of Panic Disorder with or without Agoraphobia and must have been willing to undergo a 5-session course of breathing training and accept the possibility of an 8-week treatment delay if assigned to the waitlist group. People with a history of schizophrenia, bipolar disorder, dementia, alcohol or drug abuse in the preceding year and/or current use of recreational drugs or more than 15 alcoholic drinks per week, a current score on the Beck Depression Inventory exceeding 30, or current suicidality were excluded. Moreover, subjects who had to be maintained on drugs with pronounced sympathetic, parasympathetic (e.g. beta-blockers, tricyclic antidepressants), or respiratory effects (e.g. bronchodilators), or those who used short-acting benzodiazepines (e.g. alprazolam) in excess of 2.0 mg/day in the preceding month, or longer-acting benzodiazepines or shorter-acting anxiolytics in the two weeks prior to evaluation were not included. Patients taking selective serotonin reuptake inhibitors (SSRIs), other antidepressants, or short-acting benzodiazepines less than 2.0 mg/day must have been on a stable dose for the duration of the study or have stopped taking the medication while participating. Medical reasons for exclusion were pregnancy, history of myocardial infarction, congestive heart failure, clinically significant asthma, emphysema, or a blood pressure above 160/100.

The EA patients were a more broadly defined chronically anxious population with anxiety attacks. The main complaint of these patients was subclinical panic attacks (episodic anxiety attacks) either as part of a DSM-IV disorder or as the sole complaint (in which case patients were diagnosed with Anxiety NOS). DSM-IV defines limited symptom attacks as having fewer than 4 of the panic attack symptoms. However, we specified that at least 2 symptoms had to be present in order to qualify as an episodic anxiety attack. Furthermore, these attacks could have been expected or unexpected, did not have to develop abruptly, and could have lasted for minutes up to several hours. The same exclusion criteria applied to this group as to the PD patients with one exception: if unexpected full-blown panic attacks were experienced, they had to be related to a disorder other than PD. Inclusion criteria for controls were the same as those of PD and EA patients, except that controls could have not met current criteria for any psychiatric disorder.

Participant Characteristics

Twenty NAC, 45 PD, and 39 EA patients participated in the current study. Six (13 %) PD and four (10 %) EA patients dropped out between initial assessment and the one-month follow up. Furthermore, 2 control subjects (10%), 13 (28.9 %) PD and 4 (10.3 %) EA patients were unable to raise their CO_2 above baseline during hypoventilation, whereas all participants were able to lower their CO_2. One PD patient had to stop the procedure because it was too anxiety-provoking, and one EA patient was unable to undergo the tests due to high blood pressure. All subjects who reacted contrary

to the instruction of the initial hypoventilation test, i.e., decreased instead of increased their pCO_2, were excluded from the analyses of the psychophysiological data. A total of 18 controls, 31 PD, and 32 EA patients remained. People who complied with the instructions and those who did not, were comparable on demographic and clinical variables.

Table 1

Demographic Characteristics by Group

	PD (N = 45)	EA (N = 39)	NAC (N = 20)	χ^2, *z,* or *F* - ratio	*p*
Women (%)	66.7	68.6	55.0	$\chi^2 = 1.13$	$p = 0.57$
Age (years)	41.8 (12.7)	46.7 (11.2)	45.7 (12.5)	$F = 259.92$	$p = 0.18$
BMI (kg/m^2)	25.5 (4.66)	23.4 (3.93)	25.4 (4.03)	$F = 2.71$	$p = 0.07$
Fitness level (0-3)[a]	31.42	52.9	54.7	$\chi^2 = 19.05$	$p = 0.00$
Ethnicity (%)					
Hispanic	15.6	5.13	5.00	$\chi^2 = 5.76$	$p = 0.22$
Not Hispanic	51.1	69.2	90.0		
Declined to report	17.8	7.69	5.00		
Missing	15.6	7.69	0.00		
Race (%)					
Caucasian	40.0	51.3	60.0	$\chi^2 = 9.20$	$p = 0.51$
African-American	2.22	25.6	0.00		
Asian	13.3	13.9	30.0		
Native Hawaiian or other Pacific Islander	4.44	0.00	0.00		
More than one race	4.44	5.13	0.00		
Declined to report	15.6	0.00	10.0		
Missing	20.0	12.8	0.00		

Note. Values are expressed as percentages, means (standard deviations), or mean ranks; PD = Panic Disorder; EA = Episodic Anxiety; NAC = Non-anxious Controls; BMI = Body Mass Index; χ^2 from contingency tables; [a]0 = not very active, 1 = weekend exerciser, 2 = at least 1-2 times a week active, 3 = 3 or more times a week active, *F* values from one-way ANOVAs.

Groups were matched on age, sex, body mass index, race, and ethnicity (see Table 1). Non-anxious controls had a mean age of 45.7 years and were 55% women. The PD and EA group's mean ages were 41.8 years with 67% women and 46.7 years with 69% women, respectively. However, the PD patients were less active than EA patients and NAC, who did not differ from each other. The majority of the panic group was diagnosed with PD with Agoraphobia (62.2%), in all of whom of mild to moderate severity. EA patients mostly suffered from Anxiety NOS (38.5%), also with mild to moderate severity. About one third of the PD (37.8%) and EA (38.5%) patients had an additional DSM-IV diagnosis. A complete list of all primary diagnoses and comorbidities can be found in the appendix.

Fifty-three percent of PD, 69% of EA patients, and 50% of the NAC were taking medication on a regular basis and had often more than one kind. Twenty-two percent of PD patients were taking anxiolytics (8, benzodiazepines; 2, buspirone), 2% beta-blockers (1, propanolol), 2% non-sedating antihistamines (1, fexofenadine), and 33% took antidepressants (10, SSRIs; 1, tricyclic antidepressants; 2, venlafaxine; 1, bupropion; 1, mirtrazapine). Thirty-three percent of the EA patients were taking anxiolytics (13, benzodiazepines), 8% antihistamines (1, fexofenadine; 1, loratadine; 1, cetirizine), and 23% antidepressants (5, SSRIs; 2, bupropion; 2, venlafaxine; 1, nortriptyline). Five percent of NAC were taking anxiolytics (1, benzodiazepines) and 5% antihistamines (1, claritin). Thyroid medication was taken by 9% of PD patients and 10% of NAC. Twenty percent of PD patients, 51% of EA patients, and 40% of NAC were taking other medication with no effects on our physiological recordings and hence not listed in detail.

Procedure

Potential subjects were screened over the phone with questions about their mental and physical health to check for initial eligibility. At the first visit, subjects gave written informed consent and afterwards were administered diagnostic interviews and underwent the psychophysiological assessment (see below). Patients were randomly assigned to either one of two immediate treatment groups or a waiting list (WL). Immediate treatment groups began therapy one week after the initial assessment; the WL had a waiting period of 8 weeks. The same psychophysiological assessment was conducted one month after completion of the therapy and eight weeks after the initial assessment for NAC and WL patients to match the time.

Treatment

Therapy consisted of five weekly sessions of biofeedback-assisted breathing training and practice of breathing exercises at home on a daily basis. Patients were randomly assigned to one of two therapy groups: hypercapnic (Raise-CO_2)[1] versus hypocapnic (Lower-CO_2)[2] breathing. The first treatment was based on the theory that HV causes or contributes to panic attacks; the latter on the opposite assumption, namely that high CO_2 causes or contributes to panic attacks. Both therapeutic approaches were comparable on important variables such as duration of therapy, patient-therapist interaction, direction of attention to bodily sensations, goal of regular breathing, use of a

[1] In the following, we will refer to this group as "Raise".
[2] In the following, we will refer to this group as "Lower".

capnometer, and plausibility of the treatments - only the target pCO_2 level was different. The breathing training was applied by graduate students from a local graduate school of psychology, a graduate student in a German psychology program, and a licensed psychologist.

Treatment included education on the physiology of breathing and anxiety, the rationale of the particular treatment (hyperventilation theory or suffocation false alarm theory), and review of the homework breathing exercises. Patients conducted the exercises at home twice a day using a portable capnometer (Tidal Wave Sp, Model 715, Novametrix Medical System Inc.) with an internal memory that samples exhaled gas drawn from a nasal cannula and records end-tidal pCO_2, RR, HR, and oxygen saturation. The breathing exercises consisted of three parts: a 2 minute baseline, 10 minutes of paced breathing by an audiotape, and another 5 minutes of breathing in a different way (depending on the therapy condition) without a pacing aid. The tone pattern of the audiotape was set to correspond to 9 breaths per minute with rising tones indicating inhalation and falling tones, exhalation. During the last two parts, patients were supposed to breathe more deeply or shallowly to reach the required target pCO_2 level of 30 mm Hg (Lower condition) or 40 mm Hg (Raise condition), respectively, while getting visual feedback from the capnometer. Levels much lower than 30 or higher than 40 were discouraged since they are hard to maintain and can lead to unpleasant physical sensations of dizziness or shortness of breath. After each part of the exercise, patients filled out a breathing log that asked about their psychological symptoms and physical sensations on 21 items. Once breathing exercises were carried out properly, patients were encouraged to apply the breathing whenever they felt anxious or panicky.

Psychological Assessment

Diagnostic Interviews

A multi-modal assessment battery was administered to all participants that consisted of clinician-administered as well as self-rated measures. On the day of the assessments, participants underwent the Structured Clinical Interview for DSM-IV-TR AXIS I Disorders - Research Version (SCID-I; First, Gibbon, Spitzer, & Williams, 2002). PD patients were additionally given the Panic Disorder Severity Scale (PDSS; Shear et al., 1997), a clinician-rated instrument that assesses severity of PD. EA patients were interviewed and rated on the Episodic Anxiety Scale (EAS, unpublished, see appendix). The EAS was modified by Walton T. Roth from the PDSS. It consists of 9 questions asking about full-blown and subclinical panic attacks, their duration, predictability and distress, as well as about anticipatory anxiety, agoraphobic avoidance, and impairment in work and social life.

Questionnaires

Subjects completed a battery of self-report questionnaires during both assessments. A brief summary of each inventory follows.

Customized Mood Questionnaire (CMQ): The CMQ consists of 17 items that are rated each on an 11-point scale from 0 (not at all) to 10 (extremely). Items include physical sensations and psychological symptoms (for list see appendix).

Anxiety Sensitivity Index (ASI): The ASI was developed by Peterson & Reiss (1993) and includes 16 questions related to fears, worries, and concerns about anxiety and related somatic sensations that are rated on a five-point Likert scale ranging from 0 (very little) to 4 (very much).

Mobility Inventory for Agoraphobia (MI): The MI (Chambless, Caputo, Jasin, Gracely, & Williams, 1985) is a 27-item inventory for the measurement of agoraphobic avoidance behavior and frequency of panic attacks. Avoidance is assessed with 26 questions and rated for both when the subject is alone and accompanied. These two factors are analyzed separately.

Beck Depression Inventory (BDI): The BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) is the most widely used self-report instrument to measure depression. It consists of 21 items rated from 0 to 3 and one question with a yes-no answer.

Physiological Assessment

After the diagnostic interviews, subjects were led to the laboratory where the testing took place in a sound-attenuated chamber while they were seated in a comfortable recliner chair. Electrodes were attached and a calibration procedure performed. After that, participants went through a procedure consisting of two normal breathing periods, a relaxation test, a voluntary hyperventilation test (VHT), and a voluntary hypoventilation test (VHO). This paper only focuses on the latter two; results of the others will be reported elsewhere.

Respiratory Challenges

The VHT consisted of three segments: a 1 minute baseline, 3 minutes of hyperventilation, and an 8 minute recovery period. Participants were instructed to lower and maintain their end-tidal pCO_2 as close as possible to 20 mm Hg. During the fast breathing, they were paced by an audiotape at 18 breaths per minute and received feedback from the investigator about their current pCO_2, and if necessary, told to breathe more shallowly or deeply in order to reach the target; about every 30 seconds if the pCO_2 was stable at the target, otherwise more frequently. The tone on the audiotape varied in pitch with an increase indicating inhalation and decrease, exhalation. To minimize interpersonal influences, the participants could not see the investigator during the test itself.

The VHO consisted of the same segments as the VHT but instead of lowering the pCO_2, participants were instructed to raise it above baseline while being paced at 6 breaths per minute. Every breath began with two seconds of inhalation, followed by seven seconds of paused breathing, and in the last second, quick and strong exhalation. Subjects were also given feedback about their current CO_2 level during this test.

Before and after both tests, participants filled out the CMQ. They rated their symptoms before the start of the respiratory challenges (baseline) and then retrospectively for how they had felt during the paced breathing and during the end of recovery. Moreover, they were asked about the occurrence of a panic attack at any point of the test, as well as difficulty and discomfort of the tests compared with the other.

Physiological Data reduction

Physiological recordings were analyzed with customized software written by Ansgar Cornad in MATLAB® (MathWorks, Natick, MA, USA). Mean levels of every measure were calculated for 1 min periods. Measurements more than two standard deviations below or above the average for all subjects in that condition and group were excluded from statistical analysis as outliers. The following channels were recorded:

1. End-tidal pCO_2 was measured continuously by a capnograph (Nellcor, Pleasanton, CA, USA) at a 125 Hz sampling rate, from air drawn from the nostrils through a 1.2 mm diameter plastic tube (Adult Nasal CO_2 sample line, Salter Labs, Arvin, CA, USA). End-tidal pCO_2 was determined as the level at which pCO_2 stopped rising at the end of expiration (final maximum). Expirations in which the pCO_2 waveform did not reach a plateau were deleted and replaced by linearly interpolated values. A distinct plateau was defined as having values of less than 3 mm Hg below the final maximum for the last 0.25 sec of expiration.

2. Two channels of respiration were sampled at 125 Hz from non-restrictive elastic pneumatic belts (James Long Company, Caroga Lake, NY, USA) placed around the rib cage of the thorax and the abdomen. Belt expansion was converted to volume based on thoracic belt expansions during the calibration procedure while inflating and deflating a fixed volume bag. Respiration rate (RR, breaths per minute) and tidal volume (VT, volume of air inhaled with each breath) were calculated. Furthermore,

the root mean square of successive VT and RR were calculated as tidal volume instability (VTI) and respiratory rate instability (RRI).

3. Heart rate (HR) was measured from an electrocardiogram sampled at 20 Hz. Electrodes were placed below the left and right collarbone. Artifacts were excluded by visual inspection of the recorded data. Respiratory sinus arrhythmia (RSA_{TF}) was computed based on transfer functions from cross-spectral analysis between HR and RR. RSA_{TF} values were excluded if spectral coherence between VT- and RR-interval was lower than 0.5 since that would indicate sources of variance other than respiration (Rottenberg, Wilhelm, Gross, & Gotlib, 2002).

4. Skin conductance level (SCL, EDA Isotonic Gel Electrodes, BioPac Systems) was sampled at 125 Hz after a 15 minute stabilization period and analyzed with our usual methods (Roth, Wilhelm, & Trabert, 1998). Non-specific conductance fluctuations (NSFs) were defined as changes in SCL from consecutive zero-slopes exceeding 0.2 μSiemens (Roth, Wilhelm, & Trabert, 1998).

Statistical Analysis

Patients and controls were compared on a number of self-report and physiological measures using the Statistical Package for Social Sciences (SPSS for Windows, version 15.0, SPSS Inc.).

Demographic and Clinical Measures

Differences in categorical variables such as gender or ethnicity were tested with the Kruskal-Wallis or chi square test, depending on whether categories were ordered. Continuous variables such as age, PDSS, EAS, or ASI were investigated with one-way analyses of variance (ANOVA). Initial and follow-up scores on the questionnaires were analyzed using repeated measures ANOVA with the factors Group (PD, EA, NAC) and Time (initial assessment, follow-up). Statistical significance was set to $p \leq .05$, two-tailed.

Pre-treatment

Occurrence of panic attacks was analyzed with chi-square tests. For analysis of the repeated psychological and physiological data collected during the respiratory challenges, the recommendations of Bagiella, Sloan, and Heitjan (2000) for analyzing psychophysiological data were followed. We used mixed-effects models fitted by maximum likelihood and assuming first-order autoregressive variance covariance structures with homogenous variances (AR1) to examine potential main effects or interactions. Factors were entered as fixed effects. Significant effects were followed up with Fishers LSD (least significant difference) statistic.

Psychological data were collected at three time points. Hence, each item on the CMQ was analyzed with Group (PD, EA, NAC) x Time (baseline, paced breathing, recovery) x Condition (HV, HYPO) mixed-effect models. Physiological data were first investigated separately for all three segments of the respiratory tests. At *baseline,* data

were analyzed with Group (PD, EA, NAC) x Condition (HV, HYPO) mixed-effect models. During *paced breathing,* Time (min 1, 2, 3) x Group (PD, EA, NAC) x Condition (HV, HYPO) models were used. During *recovery*, analyses were run similar to the paced breathing segment except for using 8 instead of 3 minutes for the Time factor. Second, an *overall* analysis was conducted with the baseline, last minute of paced breathing, and last minute of recovery with the factors Time (baseline, paced breathing min 3, recovery min 3) x Group (PD, EA, NAC) x Condition (HV, HYPO). Comparisons were made between PD, EA, and NAC. Furthermore, Raise, Lower, and WL of each patient group was compared with each other to test for pre-treatment compatibility. This analysis was chosen instead of an analysis of covariance, since we found that the assumptions for the latter were violated, yet we wanted to consider changes from baseline to paced breathing and recovery.

Change with treatment

Data collected during the second laboratory assessment were compared to data collected the first assessment in an analysis analogous to that of the pre-treatment measures with the addition of a factor for progress. Psychological data were analyzed with Group (PD, EA, NAC) x Time (baseline, paced breathing, recovery) x Condition (HV, HYPO) x Progress (pre-treatment, post-treatment) mixed-effect models. Physiological data at *baseline* were analyzed with Group (PD, EA, NAC) x Condition (HV, HYPO) x Progress (pre-treatment, post-treatment) mixed-effect models. During *paced breathing,* Time (min 1, 2, 3) x Group (PD, EA, NAC) x Condition (HV, HYPO) x Progress (pre-treatment, post-treatment) models were used. During *recovery*, analyses

were run similar to the paced breathing segment except for using 8 instead of 3 minutes for the Time factor. The *overall* analysis was conducted with the factors Time (baseline, paced breathing min 3, recovery min 3) x Group (PD, EA, NAC) x Condition (HV, HYPO) x Progress (pre-treatment, post-treatment). Comparisons were made between PD Raise, PD Lower, PD WL, EA Raise, EA Lower, EA WL, and NAC.

Effect Size Calculations and Adjustments for Multiple Tests

To minimize alpha inflation, we considered only a small number of variables to be primary measures, namely, those that had distinguished patients and controls in our previous study (Wilhelm, Gerlach, & Roth, 2001); remaining measures were considered secondary. The following self-report and physiological variables were primary: PDSS, EAS, CMQ-anxiety, CMQ-shortness of breath, CMQ-dizziness, CMQ-tingling sensations, end-tidal pCO_2, HR, VTI, and SCL. For these measures, the criterion for statistical significance was $p \leq .05$, two-tailed. For the secondary measures the probability was set at $p < .01$, two-tailed.

Effect sizes (ESs) were calculated as Cohen's d (Cohen, 1988) when appropriate. For Group x Progress comparisons, difference scores (e.g., pre- versus post-treatment) were computed and means and standard deviations of the differences per group entered into Cohen's equation ($d = M_{Group\ A} - M_{Group\ B}/SD_{pooled}$). For all computations, SPSS 15.0 was used. The criterion for statistical significance was $p \leq .05$, two-tailed.

RESULTS

Missing Data

For both assessments, 8 PD and 4 EA patients had to be excluded from analysis of cardiac measures (HR, RSA_{TF}), and one PD patient from analysis of SCL due to medications specifically affecting these variables. In addition, because of random data loss due to equipment malfunction, slightly lower Ns were used for some analysis. At initial assessment, 16 % of RSA_{TF} had to be excluded since coherences were lower than 0.5. Seven (15.6%) PD and three (7.7%) EA patients did not return their questionnaire packages. Hence, data on the clinical measures was missing for those subjects. At follow-up, 9.4% of RSA_{TF} had to be excluded due to low coherences. One (5.6%) NAC, 13 (28.9%) PD, and 3 (7.7%) EA patients did not return their questionnaire packages or dropped out.

Clinical Measures

PD patients' total score on the PDSS was 13.6 (see Table 2). In the month prior to the initial assessment, they experienced on average 8-9 full-blown panic attacks and 9-10 limited symptom episodes with severe distress, suffered from moderate anticipatory anxiety and agoraphobic fear, and mild fear of panic-related sensations. Overall, they were mildly to moderately impaired in work functioning and social life by their disorder.

The Episodic Anxiety patients had suffered from 1-2 panic attacks and 16 expected/unexpected episodic anxiety attacks in the previous month, causing moderate to severe distress.

Table 2

Clinical Measures at Pre-Treatment by Group

	PD (N = 45)	EA (N = 39)	NAC (N = 20)	*F* - ratio	*p*
Primary measures					
PDSS (0-28)	13.57 (4.21)	N/A	N/A	N/A	N/A
EAS (0-36)	N/A	15.36 (3.45)	N/A	N/A	N/A
Secondary measures					
ASI (0-64)	30.44 (11.11)	23.46 (9.51)	8.50 (5.00)	$F = 34.70$	0.00
BDI (0-63)	12.53 (7.56)	12.96 (7.75)	2.45 (2.87)	$F = 17.32$	0.00
MI-AC (0-5)	1.64 (0.57)	1.324 (0.32)	1.10 (0.19)	$F = 13.33$	0.00
MI-AL (0-5)	2.09 (0.77)	1.61 (0.71)	1.20 (0.70)	$F = 11.74$	0.00

Note. Values are expressed as means (standard deviations); ASI = Anxiety Sensitivity Index; BDI = Beck Depression Inventory; EA = Episodic Anxiety; MI = Mobility Inventory for Agoraphobia (AC = accompanied; AL = alone); NAC = Non-anxious Controls; PD = Panic Disorder; *F* values from one-way ANOVAs.

The majority of the Episodic Anxiety patients suffered from full-blown panic attacks (66.7%), which is not surprising since Barlow (2002, p.111) had noted that limited-symptom attacks rarely occur without a history of full-blown panic attacks. The episodic anxiety attacks usually had 3 symptoms and lasted 11-20 minutes. Patients were characterized by mild anticipatory anxiety, none to mild agoraphobic avoidance, and mild

to moderate impairment in work functioning and social life. Means and standard deviations for each item on the PDSS and EAS can be found in the appendix. PD patients scored highest on anxiety sensitivity, NAC scored lowest, and EA patients were intermediate (see Table 2). Scores on the BDI were equally elevated over controls in both patient groups. Agoraphobic avoidance behavior – accompanied or alone – was most pronounced in PD and equal in the other two groups.

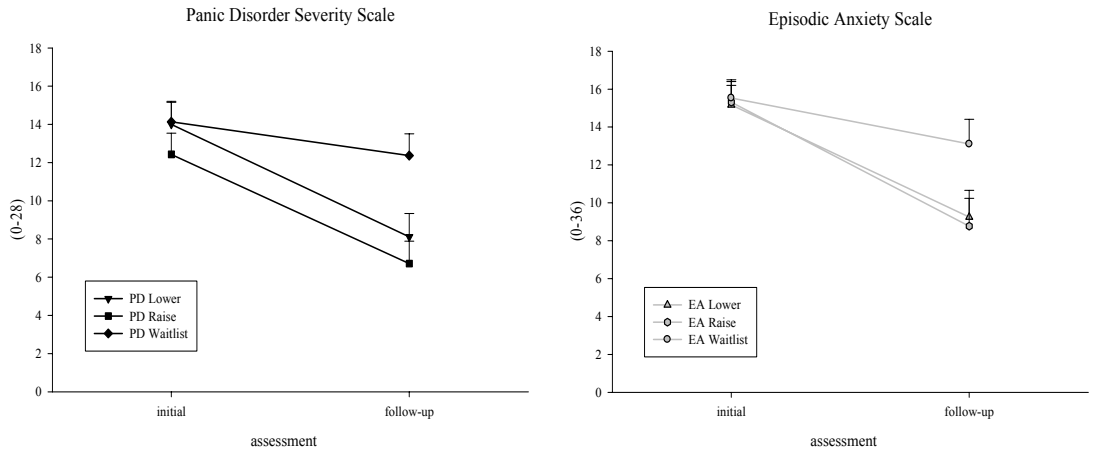

Figure 1. Means plus standard errors for the Panic Disorder Severity Scale and the Episodic Anxiety Scale at pre-treatment and follow-up.

At post-treatment, 6 (50.0%) PD patients in the Lower and 8 (61.5%) in the Raise condition no longer met criteria for PD. In the EA groups, 5 (45.5%) patients that received treatment with hypocapnic, and 2 (16.7%) of those with hypercapnic breathing, no longer met criteria for the diagnosis for which they were enrolled in the study. For instance, if an EA patient was enrolled due to experiencing anxiety attacks as part of SOP, he/she no longer met criteria for SOP after treatment. In addition, 3 (20%) WL patients in the PD and none in the EA group improved from initial to the follow-up

assessment. Furthermore, the total PDSS score decreased in the PD Lower and Raise groups to 8.12 and 6.71, respectively; EA patients' score on the EAS decreased to 9.25 in the Lower and 8.77 in the Raise group, while both WL groups remained unchanged (see Figure 1). In addition, anxiety sensitivity was lower at the follow-up assessment, but was not different between treated, waitlisted patients, and NAC. Depression decreased in all groups but waitlisted EA patients and NAC. Agoraphobic avoidance behavior did not change between assessments. Effect sizes for the primary measures ranged from 1.02 to 1.63, and for the secondary measures from -0.22 to 1.13. The results of the corresponding repeated measures ANOVAs, the effect sizes, and the numbers, means, and standard deviations are presented in the appendix.

Pre-Treatment Differences between Patients and Non-Anxious Controls

During initial assessment, the NAC increased their pCO_2 about 3.9 mm Hg (10.5 %) from baseline, PD, 3.5 mm Hg (9.9 %), and EA patients, 1.81 mm Hg (5.0 %). During the VHT, the NAC decreased their pCO_2 14.6 mm Hg (39.6 %) to 22.3 mm Hg. PD patients reached 22.8 mm Hg (decrease of 13.7 mm Hg; 37.6 %) and EA patients 21.0 mm Hg (decrease of 14.2 mm Hg; 40.3 %). In neither test, was there a difference in change between groups (VHO: $F[6,1186] = 1.26$, $p = 0.29$; VHT: $F[6,5.58] = 0.61$, $p = 0.72$). Furthermore, there was no difference in the ambient temperature in the laboratory between groups, $F(6,8.26) = 1.12$, $p = 0.36$.

During initial assessment, none of the NAC, 2 (6.5%) PD, and 3 (8.6%) EA patients experienced a panic attack during the VHO; 1 (5.6%) NAC, 7 (22.6%) PD, and 4 (12.9%) EA patients panicked during the VHT. The differences were not significant (HYPO: $\chi^2[6] = 5.78$, $p = 0.45$; HV: $\chi^2[6] = 6.04$, $p = 0.47$). Furthermore, there was a trend towards NAC and PD patients finding the VHO more difficult than the VHT, and EA patients finding the VHT more challenging. On the other hand, there was a trend towards more NAC and PD patients finding the VHT unpleasant; and EA patients finding the VHO causing more discomfort. These differences were also not significant (difficulty: $\chi^2[12] = 16.93$, $p = 0.15$; discomfort: $\chi^2[12] = 18.02$, $p = 0.12$). The results of the corresponding chi-square tests are presented in the appendix.

Comparison of the baseline, last minute of paced breathing, and last minute of recovery showed that patients overall were more anxious, $F(2,118.12) = 6.90$, $p = 001$, distressed, $F(2, 127.94) = 7.63$, $p = 0.001$, tense, $F(2, 119.85) = 9.20$, $p = 0.00$, worried, $F(2, 113.88) = 4.49$, $p = 0.13$, less relaxed, $F(2, 115.56) = 9.16$, $p = 0.00$, and felt more dizziness, $F(2, 146.07) = 5.49$, $p = 0.05$, chest pain, $F(2, 140.72) = 3.76$, $p = 0.03$, and nausea, $F(2, 108.05) = 3.21$, $p = 0.04$, than NAC. There were no differences between groups in shortness of breath, $F(2, 151.90) = 2.17$, $p = 0.12$, tingling, $F(2, 137.73) = 0.82$, $p = 0.44$, heart racing, $F(2, 140.59) = 2.32$, $p = 0.10$, sweating, $F(2, 153.36) = 1.13$, $p = 0.33$, trembling, $F(2, 161.01) = 1.42$, $p = 0.25$, chills, $F(2, 134.69) = 2.02$, $p = 0.14$, fear of losing control, $F(2, 15.48) = 0.38$, $p = 0.68$, fear of dying, $F(2, 139.79) = 0.73$, $p = 0.73$, or depersonalization/derealization, $F(2, 126.53) = 1.06$, $p = 0.35$. We found Time effects for all items on the CMQ, with the following increasing during the paced

breathing segments and decreasing with recovery in all groups: Anxiety, $F(2, 333.79) = 58.16$, $p = 0.00$, shortness of breath, $F(2, 330.24) = 82.60$, $p = 0.00$, dizziness, $F(2, 324.02) = 54.79$, $p = 0.00$, tingling, $F(2, 320.68) = 9.54$, $p = 0.00$, heart racing, $F(2, 35.72) = 53.01$, $p = 0.00$, sweating, $F(2, 334.74) = 8.75$, $p = 0.00$, trembling, $F(2, 330.91) = 5.23$, $p = 0.006$, chest pain, $F(2, 341.83) = 10.64$, $p = 0.00$, nausea, $F(2, 363.79) = 4.38$, $p = 0.013$, fear of losing control, $F(2, 331.93) = 18.67$, $p = 0.00$, chills, $F(2, 323.61) = 3.09$, $p = 0.047$, fear of dying, $F(2, 337.84) = 13.45$, $p = 0.00$, distress, $F(2, 340.97) = 53.86$, $p = 0.00$, depersonalization/derealization, $F(2, 335.05) = 13.41$, $p = 0.00$, tension, $F(2, 338.58) = 69.91$, $p = 0.00$, and worry, $F(2, 343.90) = 24.96$, $p = 0.00$. Relaxation, $F(2, 319.46) = 114.61$, $p = 0.00$, showed the opposite effect. Overall, dizziness, $F(1, 295.71) = 8.11$, $p = 0.005$, and tingling, $F(1, 293.37) = 5.66$, $p = 0.02$, were higher during the VHT than the VHO. Anxiety, $F(2, 360.53) = 3.51$, $p = 0.03$, dizziness, $F(2, 358.72) = 7.28$, $p = 0.001$, heart racing, $F(2, 366.61) = 3.19$, $p = 0.04$, and nausea, $F(2, 366.00) = 3.58$, $p = 0.03$, increased more from baseline to HV than HYPO. Furthermore, relaxation, $F(4, 319.53) = 2.53$, $p = 0.04$, fell more during the paced breathing in NAC than in patients in either test. This effect was due to higher levels in the controls to begin with. We found one Group x Time x Condition interaction for nausea, $F(4, 366.09) = 3.88$, $p = 0.004$, which was due to a greater increase in PD patients during HV than in EA patients or the NAC. We did not find any Group x Condition interactions. The results of the corresponding mixed-effects models and the numbers, means, and standard deviations are presented in the appendix. Figure 2 depicts ratings on anxiety, dizziness, shortness of breath, and tingling.

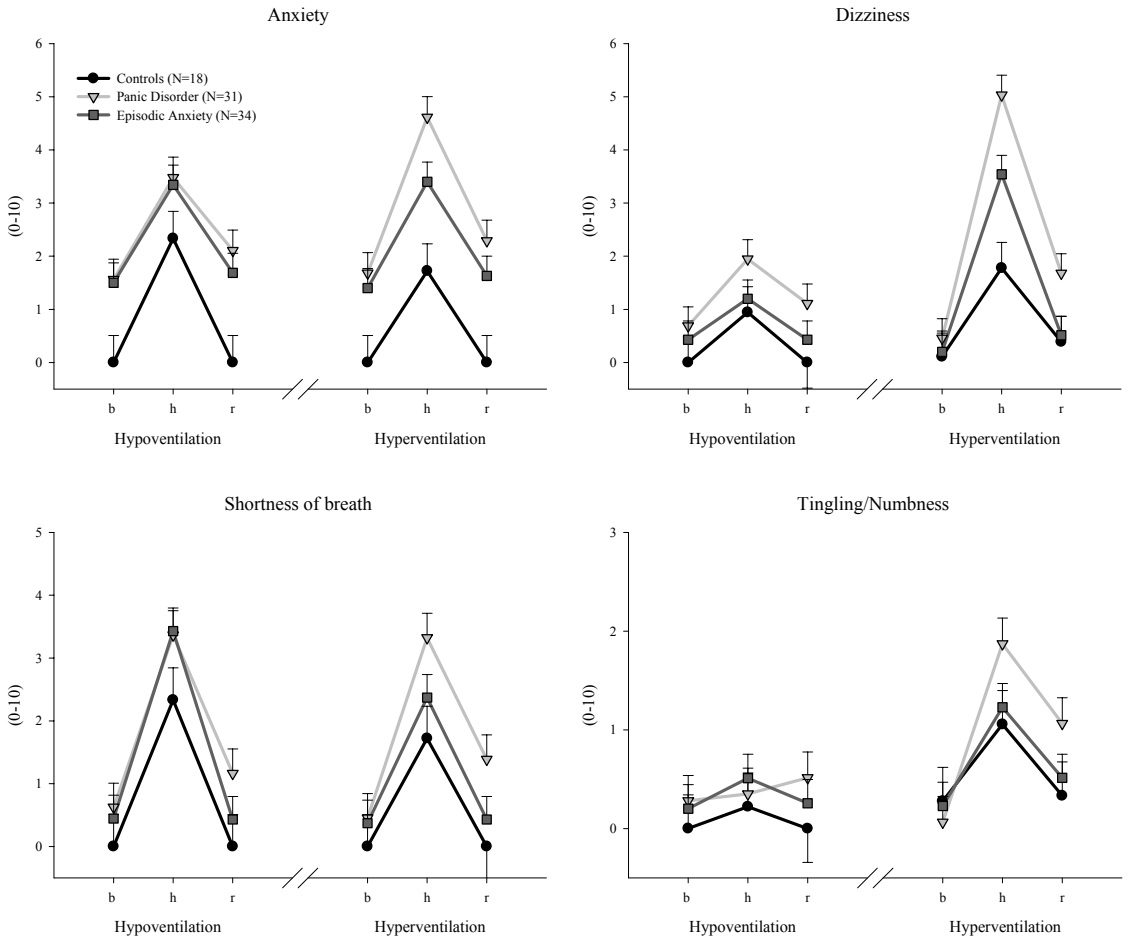

Figure 2. Means plus standard errors for anxiety, dizziness, shortness of breath, and tingling during the Voluntary Hypoventilation and Hyperventilation Test (randomized order; at baseline [b], paced breathing [h], and recovery [r]) in Panic Disorder patients, Episodic Anxiety patients, and non-anxious controls at pre-treatment.

At baseline, pCO_2 levels were lower in both conditions before HYPO across all groups, $F(1,80.24) = 6.92$, $p = 0.01$, with the greatest difference in the PD patients compared to EA patients and the NAC, $F(2,80.27) = 2.25$, $p = 0.04$ (see Figure 2). RR was highest in PD, $F(2,78.27) = 6.49$, $p = 0.002$, and overall higher before HV than HYPO, $F(1,74.98) = 5.75$, $p = 0.02$, which was due to higher values in the NAC, $F(2,75.00) = 5.23$, $p = 0.007$. Two respiratory measures, VTI, $F(2,73.92) = 4.32$, $p =$

0.02, and number of sighs, $F(2,78.81) = 5.14$, $p = 0.008$, were higher in PD than EA and NAC. VT on the other hand, was equally higher in PD and NAC than in EA, $F(2,71.79) = 3.94$, $p = 0.02$. We also found differences between the VHT and VHO: SCL, $F(1,72.00) = 4.99$, $p = 0.03$, and NSF were higher, $F(1,75.01) = 12.73$, $p = 0.001$, before HYPO compared to HV. There were no effects for RRI or the cardiac measures. *During paced breathing*, all physiological measures were different between tests, the following being higher: pCO_2, $F(1,477.52) = 1572.92$, $p = 0.00$, sighs, $F(1,278.28) = 87.63$, $p = 0.00$, and RSA_{TF}, $F(1,325.94) = 96.23$, $p = 0.00$, were lower during HV than HYPO; VT, $F(1,430.69) = 307.33$, $p = 0.00$, VTI, $F(1,382.53) = 43.53$, $p = 0.00$, RR, $F(1,203.67) = 30534.03$, $p = 0.00$, RRI, $F(1,340.92) = 43.55$, $p = 0.00$, HR, $F(1,389.09) = 111.72$, $p = 0.00$, SCL, $F(1,407.30) = 5.30$, $p = 0.03$, and NSF $F(1,447.54) = 30.09$, $p = 0.00$. pCO_2 showed a Time effect, $F(2,412.24) = 16.24$, $p = 0.00$, and a Time x Condition interaction, $F(2,382.38) = 82.28$, $p = 0.00$,: it decreased during HV and increased during HYPO in all groups. Other Time effects included fewer sighs, $F(2,306.69) = 4.73$, $p = 0.01$, and fewer NSFs, $F(2,394.21) = 12.51$, $p = 0.00$, and increasing VT, $F(2,360.14) = 4.31$, $p = 0.014$, and HR, $F(2,352.14) = 63.60$, $p = 0.00$, from minute 1 to 3 of the paced breathing segments. RRI was lower in the PD patients than both other groups, Group effect $F(2,101.60) = 3.37$, $p = 0.04$. RR showed a Group x Time x Condition interaction, $F(4,227.43) = 3.71$, $p = 0.006$, that was explained by slower breathing in the NAC during the first minute of HV. Moreover, VT was higher during HV than HYPO across all groups and lower in PD during HV than the other two groups; it also increased more during HV than HYPO (Group x Condition: $F[2,430.65] = 7.63$, $p = 0.001$; Time x Condition: $F[2,333.84] = 4.76$, $p = 0.009$). HR rose more in EA than PD or NAC from

minute 1 to 3 and overall more during HV than HYPO (Group x Time: F[4,352.14] = 2.74, p = 0.03; Time x Condition: F[2,328.60] = 14.37, p = 0.00). SCL showed in a Time x Condition interaction due to a fall during HYPO and a rise during HV. The Group x Time x Condition interaction for number of sighs, F(4,339.52) = 3.81, p = 0.005, was due to different changes in the groups over time: during HYPO, NAC and PD had fewer sighs during minute 2 compared to minute 1 and 3, while EA patients showed the opposite; and at the end of the HV segment, EA and NAC had fewer, and PD more, sighs. *During recovery*, pCO_2, F(7,1129.66) = 57.37, p = 0.00, RR, F(7,1033.32) = 3.26, p = 0.002, and RSA_{TF}, F(7,775.19) = 3.37, p = 0.002, rose; VT, F(7,964.44) = 13.93, p = 0.00, VTI, F(7,823.41) = 10.48, p = 0.00, HR, F(7,1027.35) = 14.92, p = 0.00, sighs, F(7,772.33) = 15.90, p = 0.00, SCL, F(7,1048.78) = 54.11, p = 0.00, and NSF, F(7,896.52) = 32.66, p = 0.00, fell with time in all groups (see Figure 2). End-tidal pCO_2, F(1,831.03) = 144.80, p = 0.00, RR, F(1,416.58) = 5.80, p = 0.02, and NSF, F(1,248.06) = 7.23, p = 0.008, were higher. RRI, F(1,292.18) = 4.13, p = 0.04, was lower during recovery from HYPO than HV. RR was the only measure that was different between groups, being lowest in the EA patients and equal in the two other groups, F(2,109.75) = 3.66, p = 0.003. We found two Time x Condition interactions: pCO_2, F(7,1157.71) = 24.65, p = 0.00, rose and HR, F(7,1028.53) = 5.18, p = 0.00, fell more during recovery from HV than HYPO. Furthermore, VTI, F(14,835.48) = 2.07, p = 0.012, and number of sighs, F(14,772.80) = 4.03, p = 0.00, showed a greater decrease in PD than EA patients and the NAC during recovery; RRI, F(14,950.29) = 2.60, p = 0.001, increased mildly in the controls but not the patients. We found neither Group effects, nor Group x Condition or Group x Time x Condition interactions. The results of the corresponding mixed-effects models and the

numbers, means, and standard deviations are presented in the appendix. Figure 3 depicts the end-tidal pCO_2 and heart rate during both tests.

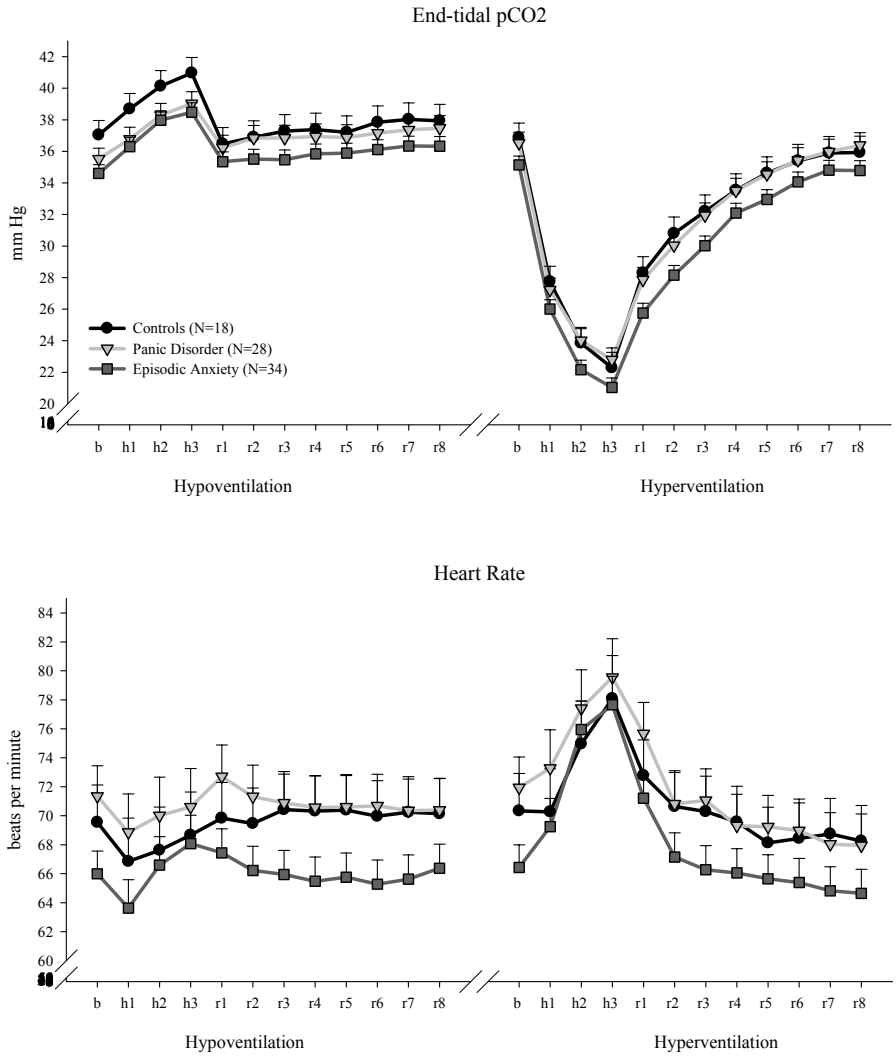

Figure 3. Means plus standard errors for end-tidal pCO_2 and heart rate during the Voluntary Hypoventilation and Hyperventilation Test (randomized order; at baseline [b], 3 min paced breathing [h], and 8 min recovery [r]) in Panic Disorder patients, Episodic Anxiety patients, and non-anxious controls at pre-treatment.

The *overall analysis* showed that PD patients had the highest RR, EA the lowest, and NAC was intermediate, $F(2,114.74) = 6.94$, $p = 0.001$. Number of sighs was also higher in the PD over both other groups, $F(2,159.71) = 5.25$, $p = 0.006$. Across both tests, HR, $F(2,358.38) = 87.34$, $p = 0.00$, VT, $F(2,306.80) = 51.69$, $p = 0.00$, VTI, $F(2,264.68) = 5.63$, $p = 0.004$, SCL, $F(2,360.94) = 141.00$, $p = 0.00$, and NSF, $F(2,332.30) = 70.32$, $p = 0.00$, rose with paced breathing and fell with recovery; CO_2, $F(2,386.78) = 423.26$, $p = 0.00$, RR, $F(2,269.22) = 10.00$, $p = 0.00$, and RRI, $F(2,242.42) = 64.02$, $p = 0.00$, fell with the second segment and rose again with recovery. We found some differences between conditions: pCO_2, $F(1,441.56) = 254.32$, $p = 0.00$, RSA_{TF}, $F(1,257.82) = 11.35$, $p = 0.001$, and sighs, $F(1,275.73) = 5.99$, $p = 0.02$, were overall higher and RR, $F(1,261.45) = 189.92$, $p = 0.00$, VT, $F(1,308.00) = 55.97$, $p = 0.00$, and HR, $F(1,417.95) = 7.64$, $p = 0.006$, were lower during the VHO than the VHT. Several significant Time x Condition interactions occurred: the interaction for pCO_2, $F(2,366.45) = 1040.24$, $p = 0.00$, and sighs, $F(2,341.28) = 17.46$, $p = 0.00$, were due to lower levels during HV but higher levels during HYPO compared to its baselines and recoveries. RSA_{TF}, $F(2,290.70) = 24.28$, $p = 0.00$, RR, $F(2,324.76) = 284.78$, $p = 0.00$, VT, $F(2,37.86) = 125.77$, $p = 0.00$, VTI, $F(2,308.67) = 5.47$, $p = 0.005$, and HR, $F(2,331.16) = 79.43$, $p = 0.00$, showed exactly the opposite effect: they decreased from baseline to HYPO and increased to HV. SCL, $F(2,334.06) = 9.43$, $p = 0.00$, and NSFs, $F(2,366.15) = 15.33$, $p = 0.00$, rose more from baseline to HV than to HYPO. Furthermore, RR, $F(4,269.64) = 3.84$, $p = 0.005$, and VTI, $F(4,265.01) = 5.90$, $p = 0.00$, changed more in PD than in EA or NAC. HR,$F(4,358.48) = 3.11$, $p = 0.02$, changed more in the two patient groups, while VT, $F(4,307.01) = 3.91$, $p = 0.004$, changed least in PD from baseline, last minute of paced

breathing, to the last minute of recovery. The overall analyses did not yield any Group x Condition interactions. The results of the corresponding mixed-effects models and the numbers, means, and standard deviations are presented in the appendix.

Pre-Treatment Differences between Raise, Lower, and Waitlist Patients

At initial assessment, PD patient treatment groups did not differ on demographic variables or any of the clinical measures. During the psychophysiological assessment, patients in the Lower condition feared losing control less than the other two groups, $F(2,59.38) = 3.14$, $p = 0.05$. The WL on the other hand felt least relaxed, $F(2,46.57) = 4.48$, $p = 0.02$. Fear of dying, $F(4,151.78) = 2.84$, $p = 0.03$, increased more in the WL and Lower during paced breathing than in the Raise group. The Group x Time x Condition interaction for trembling, $F(4,152.83) = 2.99$, $p = 0.02$, was explained by a greater rise in the WL during HYPO and less during HV than the other two groups.

For the physiological measures, there were few effects. RR and RRI showed main effects and interactions. Effects for RR (baseline: Group, $F(2,30.40) = 3.22$, $p = 0.05$; paced breathing: Group, $F(2,47.80) = 4.46$, $p = 0.02$, Group x Time, $F(4,95.50) = 2.83$, $p = 0.03$, Group x Time x Condition, $F(4,107.76) = 3.23$, $p = 0.02$; overall: Group, $F(2,40.75) = 4.66$, $p = 0.02$, Group x Time, $F(4,109.27) = 6.43$, $p = 0.00$) were explained by highest values in the Lower group that fell more during HYPO and rose less during HV. RRI was highest during the VHO baseline and lowest during the VHT baseline in

the Raise group but consistently higher during the paced breathing segments with the greatest values during the first minutes (baseline: Group x Condition, $F(2,24.83) = 3.53$, $p = 0.05$; paced breathing: Group, $F(2,30.23) = 9.82$, $p = 0.001$, Group x Time, $F(4,91.31) = 3.97$, $p = 0.005$; overall: Group x Time x Condition, $F(4,113.57) = 2.69$, $p = 0.03$). Furthermore, VT was highest during HV in the WL, $F(2,146.28) = 3.34$, $p = 0.04$, and NSF, $F(2,61.38) = 3.77$, $p = 0.03$, was lowest in the Raise group during recovery which also caused the Group x Time interaction in the overall analysis, $F(4,109.07) = 2.57$, $p = 0.04$. VTI was highest in the WL at the VHO baseline and highest in the Lower group at VHT baseline, $F(2,27.50) = 3.50$, $p = 0.04$. During the paced breathing, VT increased across both conditions only in the Raise group, $F(2,146.28) = 3.34$, $p = 0.04$. The results of the corresponding mixed-effects models and the numbers, means, and standard deviations are presented in the appendix.

EA patients were matched on most demographic and clinical measures. However, the WL had higher scores on the ASI than both immediate treatment groups, $F(2,559.60) = 9.15$, $p = 0.001$, and the Lower group had lower scores on the BDI than the WL, however, Lower and WL were both not different from Raise, $F(2,218.74) = 4.39$, $p = 0.02$. During the psychophysiological assessment, the WL scored overall higher on anxiety, $F(2,53.92) = 4.15$, $p = 0.02$, tingling, $F(2,72.48) = 5.36$, $p = 0.01$, and chills, $F(2,72.23) = 4.26$, $p = 0.02$.

Among physiological measures, we found five interactions (Group x Time for RR, Group x Condition and Time x Condition for RRI, Group x Condition for VTI, Group x Time x Condition for sighs) during the paced breathing segments: RR,

$F(4,100.90) = 4.99$, $p = 0.001$, was slightly higher in the Lower group during minute 2 of HYPO; RRI was in general lower in the WL during HYPO than HV, $F(1,150.89) = 10.29$, $p = 0.002$, and also slightly rose during minute 2, $F(2,150.91) = 3.35$, $p = 0.04$; VTI, $F(2,167.34) = 3.58$, $p = 0.03$, was higher in the Raise group during HV; number of sighs increased more during minute 2 of HYPO in the WL than the other two groups or HV, $F(4,147.00) = 2.58$, $p = 0.04$. During recovery, VTI showed a greater decline in the Raise group during recovery from HYPO than in the other two groups and compared to the VHT, $F(4,141.30) = 2.49$, $p = 0.05$. RRI declined slightly in the Lower and increased in the Raise group over time, $F(2,150.91) = 3.35$, $p = 0.04$, and in general greater changes took place in RRI during recovery from HV than HYPO, $F(4,141.30) = 2.49$, $p = 0.05$. Furthermore, NSF declined more in the Lower group, $F(14,279.71) = 2.78$, $p = 0.001$. There were four Group x Time interactions involving the baseline, the last minute of paced breathing, and the last minute of recovery. From baseline to paced breathing, HR $F(4,160.21) = 6.37$, $p = 0.00$, increased less in the WL; RR, $F(4,109.17) = 3.76$, $p = 0.01$, increased more in the Lower group; and pCO_2, $F(4,163.87) = 4.88$, $p = 0.001$, increased more in the Raise group.

Pre-Treatment Differences between Completers and Drop-outs

There were no differences between PD completers and drop-outs in the demographic data, clinical outcome, or psychometric measures. On physiological measures during recovery, drop-outs compared to completers had higher pCO_2 levels, $F(1,35.82) = 6.11$, $p = 0.02$, VTI, $F(1,54.86) = 4.83$, $p = 0.03$, more sighs, $F(1,116.31) =$

8.33, $p = 0.005$, and fewer NSF, $F(1,61.43) = 7.24$, $p = 0.01$, . The overall analysis also confirmed the higher pCO_2 levels, $F(1,36.11) = 4.71$, $p = 0.04$, and fewer NSFs, $F(1,55.52) = 7.15$, $p = 0.01$, in the drop-outs. Among the EA patients, there was only one drop-out who was part of the psychophysiological analysis. Hence, no comparison between completers and drop-outs were made. The results of the corresponding mixed-effects models and the numbers, means, and standard deviations for the PD patients are presented in the appendix.

Psychophysiological Change with Treatment

At the follow-up assessment, the following pCO_2 increases from baseline were observed during HYPO: NAC 4.2 %; PD Lower 5.5%, PD Raise 12.3%, PD WL 0.7%, EA Lower 12.4%, EA Raise 7.0%, and EA WL 5.1%. During HV, NAC lowered their pCO_2 42.0%, PD Lower 38.7%, PD Raise 35.4%, PD Waitlist 39.2%, EA Lower 33.0%, EA Raise 39.2%, and EA WL 40.1%. The mixed-effect models showed that the change rates were different between groups, $F(12,789.17) = 1.78$, $p = 0.05$. There was no difference in the ambient temperature in the laboratory, $F(6,265.04) = 0.99$, $p = 0.44$.

None of the NAC or PD patients, and 2 (6.3%) EA patients experienced a panic attack during the VHO; none of the controls or EA patients, and 5 (16.1%) PD patients panicked during the VHT. The differences were not significant (HYPO: $\chi^2[6] = 2.82$, $p = 0.83$; HV: $\chi^2[6] = 9.95$, $p = 0.13$). Furthermore, ratings on difficulty and discomfort of

both tests were not different between groups, $\chi^2(12) = 13.30$, $p = 0.35$. The results of the corresponding Chi-Square Tests are presented in the appendix.

For psychological variables, we found several effects for the factor Progress: anxiety, $F(1,326.88) = 13.38$, $p = 0.00$, tension, $F(1,335.94) = 10.34$, $p = 0.001$, worry, $F(1,326.84) = 4.29$, $p = 0.04$, shortness of breath, $F(1,376.89) = 3.82$, $p = 0.05$, chest pain, $F(1,335.09) = 3.74$, and heart racing, $F(1,362.78) = 8.93$, $p = 0.003$, were lower at follow-up compared to the initial assessment in all groups. Furthermore, shortness of breath, $F(2,785.79) = 3.13$, $p = 0.04$, heart racing, $F(2,795.06) = 6.77$, $p = 0.001$, and chest pain, $F(2,829.65) = 3.21$, $p = 0.04$, increased less from baseline to the paced breathing at follow-up, regardless of the condition or group. Sweating increased less at follow-up in the immediate treatment groups, $F(12,778.32) = 1.80$, $p = 0.04$. Trembling was higher during HYPO at follow-up in the NAC, PD Lower, and PD WL, and higher during HV at follow-up in the NAC and PD WL; the EA patients did not change on that item, $F(12,816.62) = 2.70$, $p = 0.001$. The results of the corresponding mixed-effects models and the numbers, means, and standard deviations are presented in the appendix.

At baseline, pCO_2 was lower in both Lower patient groups (decreased in PD 2.31%, in EA 6.02%) and from initial to follow-up increased in both Raise patient groups (increase in PD 5.11%, in EA 4.51%) and remained unchanged in the WL groups and NAC, $F(6,289.88) = 5.49$. SCL showed a Progress effect, $F(1,200.91) = 9.23$, $p = 0.003$, due to lower levels at follow-up, a Condition x Progress interaction due to a decrease from initial assessment to follow-up across all groups before HYPO but not before HV,

$F(1,145.87) = 6.03$, $p = 0.02$, and a Group x Progress interaction due to lower levels at follow-up in PD Lower, PD Raise, EA Lower, and EA WL, $F(6,632.24) = 3.49$, $p = 0.005$. NSFs were also fewer at follow-up before HYPO than HV, $F(1,222.86) = 4.51$, $p = 0.04$. VT decreased in the NAC and all PD but increased in all EA patients from initial to follow-up, $F(6,294.18) = 3.49$, $p = 0.002$. RSA_{TF} fell from the first to the second evaluation in both PD immediate treatment groups and the EA WL, and rose in the EA Raise and PD WL, $F(6,252.41) = 2.46$, $p = 0.03$. *During paced breathing*, pCO_2 was lower in both Lower and higher in both Raise groups, $F(6,386.05) = 2.99$, $p = 0.007$. VTI showed a Time x Progress interaction, $F(2,754.81) = 4.79$, $p = 0.009$, and a Condition x Progress, $F(1,689.54) = 5.46$, $p = 0.02$, interaction. The first interaction was due to a decrease at minute two of the paced breathing at follow-up but not initial assessment and the latter to a general rise during HYPO but no change during HV from initial to follow-up. Values for RR changed slightly to the second assessment, $F(12,585.40) = 2.76$, $p = 0.001$: there were higher levels for PD Lower at min 3 of HYPO and min 1 of HV as well as for EA Lower at min 3 of HV, and lower levels for PD Raise at min 1 and 2 of HV, and for EA Raise at min 3 of HYPO. From the first to the second evaluation, RRI decreased during HYPO in the NAC, PD Raise, and EA Lower and even increased in the EA WL; during HV it was higher in both PD immediate treatment groups (Condition x Progress: $F[1,497.59] = 5.48$, $p = 0.02$; Group x Condition x Progress: $F[6.497.17] = 3.43$, $p = 0.003$). The Time x Progress interaction for sighs was explained by a steady decrease over time at follow-up, but an increase in minute 3 of the paced breathing at initial assessment, $F(2,664.35) = 5.90$, $p = 0.003$. Furthermore, sighs changed from the first to the second assessment during HYPO: they increased in both Lower groups and the

NAC, and decreased in both Raise groups (Group x Time x Progress: F[12,663.12] = 2.36, p = 0.006; Time x Condition x Progress: F[2,699.81] = 6.00, p = 0.003 ; Group x Time x Condition x Progress: F[12,698.36] = 2.71, p = 0.001). SCL was overall lower at follow-up, F(1,632.10) = 13.80, p = 0.00, which was caused by lower values only in both immediate PD patient groups, EA Lower, and EA WL, F(6,632.24) = 3.49, p = 0.005. *During recovery*, both Lower groups had lower and both Raise groups higher pCO_2 levels at follow-up compared to initial assessment, F(6,409.94) = 3.42, p = 0.003. SCL on the other hand was lower at follow-up in the NAC, PD Raise, and EA WL groups but higher in PD Lower, EA Lower, and EA Raise, F(6,576.33) = 2.54, p = 0.02. VT showed a smaller decrease over time during recovery from HYPO at the follow-up compared to initial and was overall lower, F(7,1979.03) = 2.22, p = 0.03. RRI was also lower at follow-up across all groups, F(1,349.29) = 11.04, p = 0.001. The last respiratory measure that yielded significant results was number of sighs with a Group x Time x Condition x Progress interaction, F(42,1618.55) = 1.61, p = 0.008: sighs changed less over time at follow-up compared to initial and were increased during recovery from HYPO at follow-up in all groups but both the two patient groups that received hypercapnic treatment, who had fewer sighs; recovery from HV showed the opposite effect for the groups (more in both Raise, fewer in all other groups). NSFs increased during follow-up in all groups, F(1,222.86) = 4.51, p = 0.04. Looking at the groups separately, PD Lower, PD WL, and both EA treatment groups had more NSF at follow-up; all other groups (NAC, PD Raise, EA WL) had fewer, F(6,222.05) = 2.47, p = 0.03. ESs for the change of resting pCO_2 levels in the immediate treatment groups vs. waitlisted patients ranged from -0.69 to 0.54. The results of the corresponding mixed-effects models, effect sizes, and the numbers,

means, and standard deviations are presented in the appendix. Figure 4 displays the end-tidal pCO_2 levels for both tests at initial assessment and follow-up.

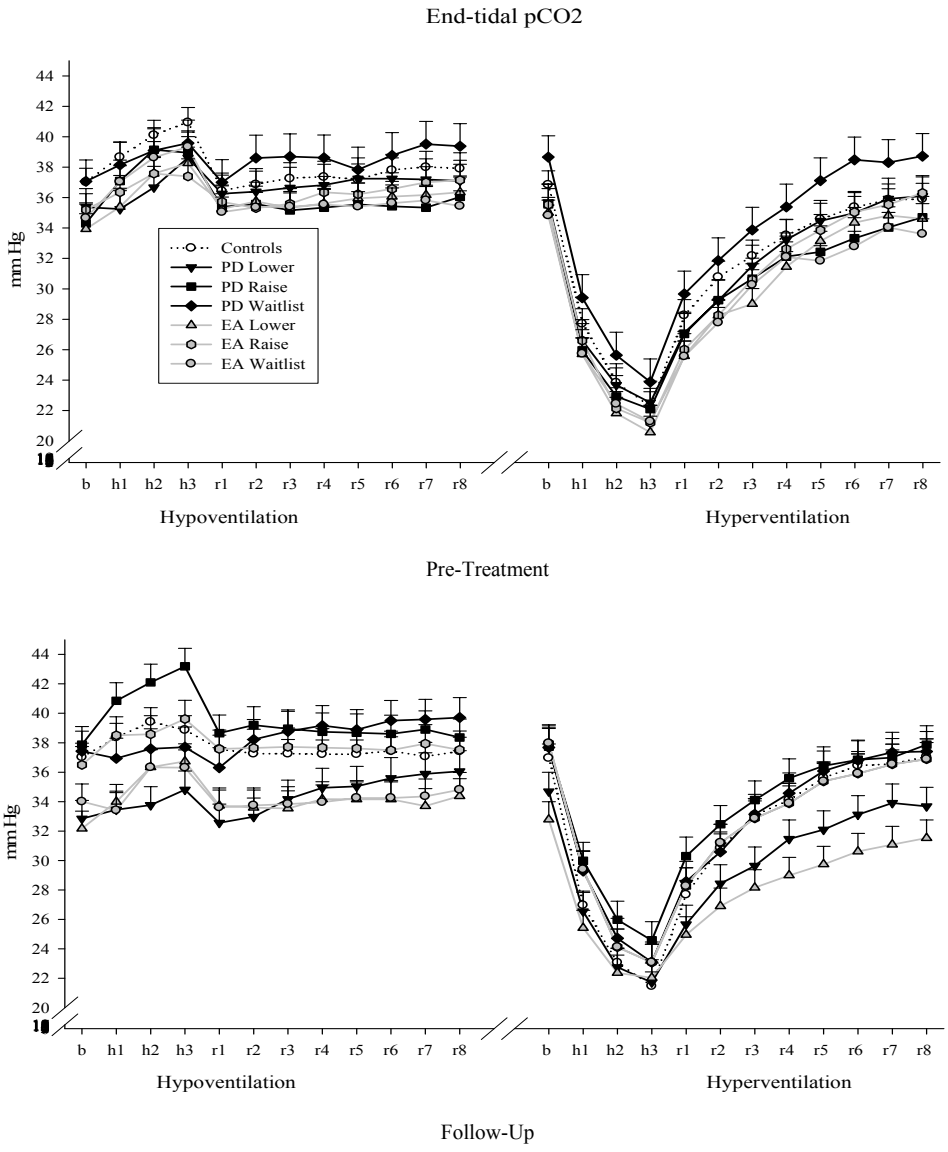

Figure 4. Means plus standard errors for end-tidal pCO_2 during the Voluntary Hypoventilation and Hyperventilation Test (randomized order; at baseline [b], 3 min paced breathing [h], and 8 min recovery [r]) in Panic Disorder patients, Episodic Anxiety patients, and non-anxious controls at pre-treatment and follow-up.

Overall analysis yielded significant results for two primary and two secondary measures. End-tidal pCO_2 decreased after treatment in both Lower groups and increased in both Raise groups; the WL and NAC did not change, $F(6,314.78) = 2.86$, $p = 0.01$. Furthermore, increase from baseline to HYPO was greater in the PD Raise and EA Lower groups, and less in PD Lower, PD WL, EA Raise, and NAC at the follow-up. Change from baseline to HV was smaller in PD Raise, EA Raise, and EA Lower, and greater in PD Lower, PD WL, and NAC, $F(12,789.17) = 1.78$, $p = 0.05$. Sighs were more frequent at follow-up than at initial assessment except for EA Raise during VHO, and more frequent during HYPO and less frequent during HV than its baselines and recoveries except for PD Raise (also had more sighs during HV than baseline and recovery) and EA Raise (had fewer sighs during HYPO), $F(12,718.73) = 2.35$, $p = 0.006$. SCL showed a Condition x Progress interaction, $F(1,622.84) = 4.34$, $p = 0.04$, explained by a greater increase from initial to follow-up in the VHT than VHO. NSF were overall fewer in PD Lower, PD WL, EA Lower, and EA Raise at follow-up and more frequent in the NAC, PD Raise, and EA WL, and showed the greatest increase from baseline to paced breathing in the EA Raise group during the VHT, $F(12,506.07) = 1.81$, $p = 0.04$. The results of the corresponding mixed-effects models and the numbers, means, and standard deviations are presented in the appendix.

The completer analysis had similar results but on higher significance levels. The results of the mixed-effects models and the numbers, means, and standard deviations are presented in the appendix.

DISCUSSION

The aim of this study was to investigate whether patients suffering from Panic Disorder or Episodic Anxiety would exhibit a greater psychophysiological response than non-anxious controls to two respiratory challenges, namely, voluntary hypoventilation and hyperventilation, and whether breathing training would attenuate these responses. These questions are important since PD has been considered a disorder with prominent respiratory abnormalities and therefore, treatment targeted at changing these abnormalities should influence the reaction to respiratory challenges. In addition, there is evidence that reactions to provocations may be more related to whether an individual has had a panic attack than to whether he or she meets the full criteria for PD. Hence, patients who are suffering from anxiety attacks might benefit from treatment with BT, regardless of their diagnosis.

Effects of Voluntary Hypoventilation and Hyperventilation

Voluntary hypoventilation and hyperventilation affected most self-report and physiological measures of both patient groups and NAC. Moreover, most self-reported variables were changed equally by the two test provocations. Both, HYPO and HV increased fear of dying, tension, worry, fear of losing control, overall distress, and sensations of shortness of breath, heart racing, sweating, trembling, chest pain, nausea, chills/hot flashes, and during both tests people felt less relaxed than at baseline or

recovery. However, overbreathing resulted in greater reports of dizziness and tingling and of a greater increase in dizziness from baseline compared to underbreathing. Anxiety increased in both conditions, but more from baseline to HV than from baseline to HYPO. PD patients showed a trend towards more anxiety during HV than the other two groups, but the three-way interaction was not significant. Furthermore, neither test was perceived as being more difficult to perform or causing more discomfort than the other, and neither provoked more panic attacks.

As expected, we found several differences between the effects of the VHO and VHT on physiological measures during the paced breathing segment. Not surprisingly, pCO_2 was different since different goals for changing it had been given to our patients. All respiratory (pCO_2, VT, VTI, RR, RRI, sighs) and activation measures (HR, RSA_{TF}, SCL) were different. Tidal volume, VTI, RR, RRI, HR, and SCL were higher; pCO_2, sighs, and RSA_{TF}, were lower during overbreathing compared to underbreathing. In order to achieve the required rise or drop in pCO_2, breathing depth and rate were lowered during HYPO and increased during HV. Other findings such as higher HR during overbreathing may have been caused by greater physical exertion and disturbance of the respiratory system, seen in higher VTI and RRI. This is consistent with numerous studies showing that HV causes an increase in HR regardless of diagnosis (Asmundson et al., 1994; Rutherford et al., 2005; Todd et al., 1995; Whittal et a., 1995). Changes in pCO_2, VT, HR, and SCL over the 3 minutes were greater during HV than HYPO. On the other hand, RSA_{TF}, an indicator of parasympathetic activation, was higher during HYPO. These findings go along with Asmundson et al.'s (1994) and Fiamma et al's (2007)

findings, two studies that directly compared HYPO and HV. The authors found that HV increased HR and breathing variability and attenuated RSA_{TF}, whereas HYPO augmented RSA_{TF} and even decreased HR and breathing variability. During recovery, deactivation was seen in both conditions: HR, RSA_{TF}, SCL, and NSF decreased over time. Not surprisingly, we found higher pCO_2 during the VHO recovery since baseline levels were achieved quicker than during the VHT. Since both pCO_2 and HR changed more during HV than HYPO, these measures also increased and declined, respectively, more during recovery from HV than from HYPO. Furthermore, RR rose and VT, VTI, and sighs fell with time, regardless of the condition. Since subjects were breathing very deeply during HV, it is not surprising that we observed fewer sighs than during underbreathing, when people were more likely to gasp for air because of lack of oxygen and a sigh could have been detected more easily with our algorithm (a sigh was defined as a breath twice the normal size). Neither result can be explained by pre-existing differences between both conditions.

Greater changes in physiological measures appeared only in overall greater dizziness and tingling during the VHT compared to VHO, and in no other self-report measures. Since baseline anxiety was the same for both tests, it is unlikely that the instruction of having to hypo- or hyperventilate caused different levels of anxiety and in turn produced different effects on physiological measures. Hence, the physiological symptoms themselves may have caused the anxiety. On the other hand, it is possible that the sensation of dizziness was sufficient to create a fear of fainting, which could have accounted for increase anxiety.

Direct comparison of HYPO and HV produced by voluntary changes of breathing has hardly been reported previously. Our results suggest that HYPO and HV without changing the composition of inhaled gases to change pCO_2 levels, result in different physiological effects during the altered breathing itself. The lower pCO_2 during recovery from HV is probably simply due to the smaller preceding change with HYPO.

Reaction to Respiratory Challenges

Our findings confirmed some of our previous results of baseline respiratory abnormalities in PD, but our pre-treatment analysis did not support our hypothesis that PD and EA patients would show a stronger psychophysiological reaction to both tests than non-anxious controls.

At baseline, both patient groups felt equally more anxious, distressed, tense, worried, and less relaxed than the NAC. With our design, we cannot address the cause of the elevated levels of anxiety before the tests. They may represent baseline anxiety (tonic arousal) or anticipatory anxiety. Of physiological measures, pCO_2 was higher before hyperventilating, which was caused by increased baseline levels in the PD patients. Since the two tests were given in an order randomized across subjects, this cannot be due to carry over effects from the previous challenge. Since a drop in pCO_2 is caused by an increase in VT and/or RR, we would have expected these differences also to be present in the PD patients. Surprisingly, VT and RR were not lower before HV. Nevertheless, some

people may have done one or the other, i.e. changed either VT or RR, which could have overwhelmed the overall Group x Condition interaction. Furthermore, baseline anxiety was not different in PD between tests. Hence, lower pCO_2 could have not represented anticipatory anxiety before underbreathing. With our recorded data we cannot explain why PD patients had a lower resting pCO_2 before HYPO.

In both conditions, RR, VTI, and number of sighs differed between groups. These 3 measures were all greater in PD than EA patients or the NAC, which confirms findings of numerous other studies showing faster breathing and breathing instability in PD under resting conditions. However, the usually associated lower pCO_2 was not observed, possibly because the differences in RR between groups were not great enough. In the NAC, breathing was faster before HV than HYPO. It is unlikely that this represented anticipatory anxiety, since self-reported anxiety was not different between conditions. SCL and number of NSFs were higher before HYPO than HV across all groups, which was not accompanied by more self-reported sweating or anxiety. This may have been caused by mechanisms unrelated to the testing procedure.

All self-reported[3] variables collected during the laboratory procedures increased from baseline to paced breathing and decreased again during recovery except for relaxation, which was lowest during the paced breathing segments, and chills/hot flashes, which did not change at all. All groups felt more anxious, tense, worried, distressed, dizzy, short of breath, sweaty, nauseated, and experienced greater fear of losing control,

[3] Time effects, Condition effects, and Time x Condition effects were described above (section "Effects of Voluntary Hypoventilation and Hyperventilation" and therefore omitted from this paragraph.

fear of dying, depersonalization/derealization, tingling, heart racing, trembling, and chest pain during the paced breathing than at baseline or recovery. In addition, anxiety and dizziness increased more during HV than HYPO, and tingling was overall higher during the VHT. Only nausea increased more in PD patients from baseline to HV compared to the EA patients and NAC. Otherwise, no Group differences were found. Both patient groups had tonically higher ratings on few items but reactivity to the tests was equivalent to controls in that we did not find any Group x Time interactions. Furthermore, the frequency of panic attacks elicited by over- and underbreathing as well as subjects' comparison of the two tests in terms of difficulty and discomfort was not different between groups. These findings go along with several studies that have shown that respiratory challenges also increase anxiety in healthy controls, even though generally less than in patients (e.g., Rapee, Brown, Antony, & Barlow, 1992; Roth, Wilhelm, & Trabert, 1998; Thyer, Papsdorf, & Wright, 1984; Wilhelm, Gerlach, & Roth, 2001). Moreover, Margraf et al. (Margraf, Ehlers, & Roth 1986) showed that after baseline differences are accounted for, the increase in anxiety was the same in PD and NAC. In our study, symptom report during HV and HYPO was associated with a change in pCO_2 but unrelated to group membership.

Physiological measures were equivalent in all groups during the paced breathing segments of the VHO and VHT. However, from minute 1 to 3, some primary and secondary variables changed. For instance, pCO_2 increased during HYPO and decreased during HV, respectively, over the entire three minutes of paced breathing. Heart rate and VT increased more over time during HV. HR furthermore changed more in EA patients

than the other two groups due to lower baseline levels, although the baseline differences did not reach significance. Tidal volume was lower in PD during HV. This result is most likely due to the greater RR the PD group had to begin with, which made it unnecessary to increase the VT so much to reach the target pCO_2 level. Number of sighs and NSFs decreased over time in both tests, but sighs were overall fewer and NSFs more during HV than HYPO. Fewer sighs during HYPO can be explained in two ways: first, as mentioned above, people are more likely to gasp for air when underbreathing, and second, the VT is much smaller and hence a smaller increase in air inhaled is required for a breath to be detected as a sigh. In addition, sighs showed a three-way interaction: they decreased during HV in the EA patients and NAC, but increased in the PD patients. The latter may have taken deeper breaths intermittently rather than evenly increasing their VT to keep their pCO_2 low. Although breathing was paced, NAC had lower RR during the first minute of HV, which represented a failure to comply with instructions, and which appeared statistically as an interaction. During recovery from over- and underbreathing, only one primary and two secondary measures changed differently between groups. Tidal volume instability and sighs decreased more in PD than the other two groups, which made the group differences from baseline disappear. Respiration rate instability also showed an interaction, which was due to a very mild increase in the NAC but not in the patients.

Often investigators have found respiratory abnormalities in PD compared to non-anxious groups or other anxiety disorders at baseline and in response to respiratory challenges. However, published results are inconsistent in that some studies found

differences in both self-report and physiology, whereas in others PD was only different from other groups in self-report measures. We confirmed baseline respiratory abnormalities in PD by showing that they had higher RR, VTI, and number of sighs. The effects for VTI and sighs disappeared with the challenges. However, RR was higher during recovery than at baseline in the NAC and EA patients, which removed the Group differences that existed at baseline. Furthermore, PD patients were less active than the other two groups, which could have resulted in HR differences. However, this was not the case and hence we do not consider it likely that differences in activity level influenced any of our results. These data suggest that in terms of breathing frequency and HR, the challenges were more distressing to the NAC and EA patients.

Unfortunately, there is little consensus on standards of a hyperventilation test, which makes comparisons between studies difficult. Studies vary greatly on variables such as breathing rate, target pCO_2 level, duration of HV, and the use of pacing aids. Hornsveld et al. (Hornsveld, Garssen, & Spiegel, 1995) examined the influence of breathing depth and rate on symptom occurrence. According to them, a minimum of 3 minutes and a pCO_2 level below 1.9 kPA (14.3 mm Hg) is required for symptoms to appear in most people. On the other hand, Fried and Grimaldi (1993) reported that symptoms begin to emerge below 30 mm Hg. Since all of these factors appear to have independent influences on the outcome, one of them may have been insufficient in our study to elicit the effects often reported previously. Most studies that found differences between PD patients and other groups, had people hyperventilate down to at least 20 mm Hg (Friedman, Mathis, Hayes, Renshaw, & Dager, 2006; Wilhelm, Gerlach, &

Roth, 2001; Maddock & Carter, 1991) or required a drop of 50% from baseline (Rapee, Brown, Antony, & Barlow, 1992). If no target pCO_2 was given, usually a high RR was required (Han, Stegen, de Valck, Clement, & van de Woestijne, 1996; Nardi, Valenca, Nascimento, & Zin, 2001, 2002; Papp et al., 1997). Antony et al. (1997) did not find any differences between groups although a drop of 50% from baseline was required. However, people only hyperventilated for 90 seconds.

Not all of our participants were able to lower their pCO_2 to the target, which resulted in a mean pCO_2 level of 22 mm Hg at the end of HV. In a recently submitted paper (Wollburg, Roth, Conrad, Meuret, & Kim, in press) we compared two levels of HV, 20 mm Hg and 25 mm Hg, and found differences in self-report only for the lower level and no differences in physiological measures at either target. However, our sample size was too small to exclude subjects who did not hyperventilate quite to 20 mm Hg. Moreover, participants did not reach their target until the last minute, which potentially reduced the actual duration of HV to as little as one minute. We would not interpret our negative findings in terms of the recovery from the challenges as evidence against existence of respiratory abnormalities in PD since differences under baseline conditions emerged. Hence, our data suggest either that the mean pCO_2 level was too high and/or the duration of the HV too short. This also would explain why the anxiety ratings during the paced breathing and recovery were lower than in other studies (e.g., Maddock & Carter, 1991; Rapee, Brown, Antony, & Barlow, 1992; Wilhelm, Gerlach, & Roth, 2001).

Hypoventilation on the other hand has been shown previously to be even more anxiety provoking than HV, but it usually was induced by inhalation of gas mixtures with higher than air CO_2 concentrations. It is obvious that the increase in CO_2 was much less in our study. However, as mentioned earlier, a criticism of those provocations is that they deliver unnaturally high CO_2 levels, which renders conclusions from them questionable. We intended to produce a state that could possibly occur naturally outside the laboratory, but failed to replicate the previously reported differences. We had thought that prolonged hypoventilation even without much elevation in CO_2, would be sufficient to bring out differences, which proved to be wrong.

In the light of our results, we are unable to draw any conclusions about the state of the suffocation alarms of our second population, the EA patients. Perhaps at higher pCO_2 levels both EA and PD patients would have reacted more than NAC. However, we did not find in EA patients the greater resting VTI, RR, or sighs that we observed in PD patients, which suggests, at least baseline respiratory abnormalities are specific to PD.

It is unlikely that difference in clinical measures were the reason that we failed to find differences between groups in response to the challenges. The PD patients scored similarly higher on anxiety sensitivity than the other two groups, similar to previous studies of PD. As in other studies, patients with multiple diagnoses were not excluded. Generally, HV has been shown to be a rather mild panicogenic agent. Although unlikely, other cognitive factors could have contributed to our outcome: participants may have felt safe in the presence of an investigator and in addition, could have attributed symptoms to

an external event rather then to a spontaneous attack. For instance, Rapee (1990) and Barlow (1988, 1991) ascribed importance to the perception of lack of control during challenges, and Sanderson et al.'s study (Sanderson, Rapee, & Barlow, 1989) has shown how a perceived influence of control attenuates the reaction to CO_2 inhalation. However, there is no reason to believe that patients felt safer in our laboratory than they would have in others.

Another possible reason for inconsistency between studies is differences in the PD sample. PD patients do not appear to be a homogeneous group, as evidenced by numerous studies that examined subgroups of PD and observed different reactions among those groups to biological challenges. One distinction that has often been made is between a respiratory and non-respiratory subtype of PD. Unfortunately, our sample size was too small to run valid analyses on such subgroups.

No physiological measure showed Time x Group interactions during recovery that might have favored one or the other respiratory theories of PD. We expected that PD patients would react differently from controls to at least one of the challenges. Perhaps target levels were too low or high, respectively, in order to bring out these differences. Although resting pCO_2 levels were not different between groups, PD patients' greater VTI, RR, and sighs can be interpreted as consistent with the Suffocation False Alarm Theory as a way to keep the pCO_2 safely below the threshold that could trigger a false alarm. On the other hand, PD patients did not feel less anxious during HV than HYPO. According to Klein, lower pCO_2 should have made them feel more comfortable.

However, it should be noted that only a subgroup of subjects was included in the psychophysiological analyses, namely, those who complied with the instructions. As a result, 2 NAC, 13 PD, and 4 EA patients had to be excluded. Significantly more subjects from the PD group were unable to hypoventilate than people from the other two groups. This can also be seen as support for Klein's theory since it is consistent with the idea that PD patients were reluctant to raise their pCO_2 due to fear of triggering a false alarm and thus a panic attack. Our data support some of Ley's assumptions as well: PD patients reacted more fearfully to HV than HYPO, and did not have higher panic rates than the other groups during HYPO. However, increase in anxiety was not different between groups and some patients did panic to HYPO.

We were able to replicate some earlier findings of irregular breathing in PD patients. Results for the EA patient group confirm that these abnormalities are specific for a diagnosis of PD. However, we did not find the expected exaggerated response to respiratory challenges or a slower recovery from it that has been shown in previous studies. Psychological variables were tonically higher during all segments of the tests; physiological measures did not differ during the paced breathing and recovery periods between patients and controls. Unfortunately, we were unable to run follow-up analyses on subgroups of PD, such as respiratory vs. non-respiratory subtypes or panickers vs. non-panickers during the test, in order to examine alternative explanations. Findings suggest that hypo- and hyperventilation induced by alteration of one's breathing are rather weak panicogenic agents. End-tidal pCO_2 levels probably have to change more from baseline to bring out group differences.

Effects of Breathing Training

We hypothesized that both treatment groups would show less psychological and physiological distress in response to the respiratory challenges after therapy. Since we failed to find an exaggerated response before treatment, only certain of our hypotheses could be tested. We confirmed that patients in the Raise condition had higher baseline pCO_2 levels after than before treatment and hence, reached higher levels during HYPO than patients in the Lower condition, who had lowered resting pCO_2 at post- compared to pre-treatment. Contrary to our hypothesis, patients given the Lower treatment also reached lower pCO_2 levels during HV than those given the Raise treatment.

Panic rates to the respiratory challenges did not change after successful treatment nor did the comparison of the two tests in terms of difficulty and discomfort. Overall, anxiety, tension, shortness of breath, and perceived heart racing were lower at the second assessment, but not differently between groups. Since these variables changed regardless of group assignment, they are most likely due to test-retest effects. Furthermore, the perception of feelings of shortness of breath and heart racing increased less from baseline to the paced breathing segments for both tests at follow-up compared to the initial assessment, also regardless of the group.

For physiological measures, both treatments affected the breathing behavior at baseline: the Lower condition led to lower and Raise to higher resting pCO_2 levels after treatment during all segments of the tests and in both PD and EA patients. Hence,

patients applied their breathing lessons outside their homework exercises. The absolute changes in pCO_2 were not different between the two patient groups. Effect size differences for the resting pCO_2 level between immediate treatment groups and wait-listed patients were moderate (d >0.5) except for the comparison of EA Lower and EA WL, which was small (d >0.2). However, we did not see corresponding changes for RR or VT supposedly necessary to produce the lower or higher pCO_2 levels. There was a trend for slower breathing rates at post-treatment, but it was not significant. Possibly with a bigger sample group differences would emerge. An explanation could be that people used different combinations of breathing rate and depth in order to produce the changes in CO_2, which may have overwhelmed the overall effects. We did not find that the two treatments affected breathing in one way. Each had specific effects: both Lower groups were able to reach lower CO_2 levels than the Raise groups, who on the other hand achieved higher levels during HYPO. This effect was not caused by different change rates within the tests but by baseline differences in pCO_2. Surprisingly, the treatments did not affect other baseline breathing parameters although normalization of, for instance, breathing rate was also targeted in the homework exercises.

The irregularities observed in PD at pre-treatment were not changed by therapy. However, during HYPO, the Lower condition had more sighs at post-treatment and the Raise condition fewer. The latter also had fewer sighs during recovery from HYPO. Since the patients in the hypercapnic group were accustomed to high pCO_2 levels, they were perhaps less likely to feel a lack for air. However, this was not evidenced in different ratings of shortness of breath, which were lower at post-treatment in both tests.

In addition, baseline VT decreased from the first to the second assessment in all PD patients and the NAC, and increased in the EA patients. These changes were not related to treatment. However, we do not know why VT changed differently in the groups since at the beginning there were no differences. Furthermore, VT was overall lower at follow-up during the recovery periods, probably due to the overall lower VT in the NAC and PD groups.

We also found a Group x Progress x Condition interaction for RRI during the paced breathing periods. Since all subjects were paced during these segments, we can only explain this result as non-compliance with the instructions at follow-up.

Two of the three activation measures (HR, RSA_{TF}) were not affected by treatment, which was not surprising since respiratory measures and not heart rate or stress activation were targeted by the therapy. Furthermore, physical activity during the tests is expected to be the same at any given assessment time. Results for HR do not go along with the declined report of heart racing at follow-up. This is an example of the dissociation of self-report and physiology. Several studies have shown that especially the report of heart racing and actual HR correlate poorly (Alpers, Wilhelm, & Roth, 2005; Margraf, Taylor, Ehlers, Roth, & Agras, 1987; Wilhelm & Roth, 1998). Nevertheless, we cannot be sure that people overreported their heart sensations at the initial assessment or underreported them at follow-up, since these sensations probably depend more on pulse pressure, the difference between systolic and diastolic blood pressure, which gives a sensation of the heart pounding more than does a fast heart rate.

As expected, BT resulted in greater symptomatic improvement than waiting. At post-treatment, all immediate treatment groups were significantly better than the WL. Effect size differences between immediate and waitlisted patients for the main outcome measures were all large ($p > 0.8$). There were no differences between treatment conditions. Looking at the diagnoses at post-treatment, 56% no longer met full criteria for PD and 31% of the EA patients no longer met criteria for the diagnosis for which they were enrolled in the study. Agoraphobic avoidance did not change from pre- to post-treatment, which may be due to the high percentage of PD patients that did not suffer from Agoraphobia.

Surprisingly, anxiety sensitivity changed equally in all groups from the first to the second assessment. Since effects for the PDSS were very large and comparable to our previous treatment study (Meuret, Wilhelm, Ritz, & Roth, in press), in which we used only the Raise condition, we also had expected the greater changes on the ASI in the immediate treatment groups compared to WL that we had seen previously. Nevertheless, although anxiety sensitivity improved in all groups, effects within the PD sample were large only for the immediate treatment groups and at a moderate level for the WL. For the EA patients, all groups showed large effects. However, ASI is only considered a measure of improvement in PD and hence, we would have not necessarily expected greater changes in the treated EA patients than EA WL.

In terms of the main outcome measures, BT was equally effective for both PD and EA patients. Hence, there is reason to believe that any disorder with panic attacks would benefit from BT, regardless of not meeting full diagnostic criteria for PD or not having

had a history of PD. Although PD is characterized by experiencing panic attacks, treatment with BT should not be restricted to that disorder. Our data indicate that experiencing subclinical panic attacks may be sufficient for benefiting from BT even when those patients do not show the same baseline respiratory abnormalities as PD.

Each treatment changed the patients' resting pCO_2 level in the direction prescribed by the particular therapy. From this it follows that there must have been mechanisms working that caused a positive treatment outcome other than mechanisms changing the tonic pCO_2 level. Nevertheless, the treatment may have still had specific effects such as focusing attention on breathing. Furthermore, our results show that a general reduction in respiratory irregularity also cannot account for the outcome. The rationale of both therapies was that dysregulated breathing is central in PD and that learning better regulation will produce clinical improvement. Since both treatments worked equally well, we cannot say which respiratory theory of PD dysregulation is more valid. Perhaps subgroups of patients may benefit more from one or the other.

In the light of our results, non-respiratory factors that were similar in both treatment groups are likely to have accounted for the clinical improvement. Aside from non-specific therapy effects such as the patient-therapist interaction, the direction of the patient's attention to bodily sensations may have worked as interoceptive exposure and facilitated cognitive restructuring by desensitization and reattribution of bodily symptoms (Craske, Rowe, Lewin, & Noriega-Dimitri, 1997). In addition, the breathing exercises may have been perceived as a 'tool', a coping method, to employ in anxious situations,

which could have reduced the expectation of anxiety escalating into a panic attack. Patients may have either gained a sense of control over their anxiety attacks by being able to apply the learned breathing exercise or have used attention to breathing as distraction.

We cannot rule out that the training worked because of non-respiratory factors. How can one ever disentangle pure cognitive components from BT? It is hard to imagine that a successful BT would fail to change cognitions about panic. Reduction of attacks by any therapy must inevitably reduce catastrophic thinking. Evidence for a more respiratory mechanism might come from findings that a respiratory subtype would benefit more from BT than the non-respiratory one. We were unable to test this in these data, but Meuret et al. (Meuret, Wilhelm, Ritz, & Roth, in press) did find that a respiratory subtype did not benefit more from an anti-hyperventilatory therapy than did a non-respiratory subtype.

Six PD and 4 EA patients dropped out before the second assessment, which resulted in slightly lower treatment effect estimates in the intention-to-treat analysis on some measures. However, this has little consequence for the validity of our results. Drop-outs did not differ on demographic or clinical measures. Differences on physiological measures did not indicate that completers were less severe in their reaction to the respiratory challenges and therefore were more likely to finish. Of course, we tested only a small number of drop-outs vs. a high proportion of completers. In addition, we assume that differences between the patient groups (Lower vs. Raise vs. WL) at pre-treatment had little effect on their comparability and on the validity of the outcome measures.

In summary, both the hypocapnic and hypercapnic treatments led to symptomatic improvement compared to waitlisted patients. As outlined above, we were unable to replicate previous findings in terms of the response to breathing challenges. However, from our results we can assert that benefits from BT accrue to those suffering from panic attacks (full-blown or subclinical) regardless of whether they meet full criteria for PD. The therapies changed tonic pCO_2 level without effects on other respiratory or psychological measures during the laboratory assessment. This indicates that BT worked by variables other than the respiratory ones that had been targeted by the treatment. Our results imply that research on BT should not be restricted to PD, but expanded to other patients suffering from anxiety attacks.

Methodological Limitations

Several limitations apply to this study. There is always a chance that different statistical methods would have led to slightly different results. We chose the mixed-effects models because it has advantages over conventional variance-analytic approaches, especially when analyzing psychophysiological data (Bagiella, Sloan, & Heitjan, 2000). First, one is able to specify variance-covariance matrices that best fit the data. Second, the mixed-effects models handle missing data more effectively by fitting them with maximum likelihood. However, each statistical approach has advantages and drawbacks. There is no perfect way to analyze such a multifaceted data set.

An issue for this study is the nature of the EA patient group. Since we wanted to explore broadly whether patients suffering from anxiety attacks regardless of their primary diagnosis would show psychophysiological similarities to PD and benefit from BT, we collected what turned out to be a very heterogeneous EA group. Hence, we cannot rule out that this may have reduced certain effects found in pure PD patients and limited our inferences from the EA group. However, it is unlikely that the inclusion of comorbid anxiety disorders that have been shown to have exaggerated responses to respiratory challenges, such as SOP, overwhelmed effects of EA patients without them, since the majority of the EA group suffered from Anxiety NOS. Furthermore, increases and decreases in pCO_2 during the challenges were insufficient to bring out group differences between NAC and PD which consequently limited a more detailed investigation of the EA patients. Using pCO_2 targets relative to subjects' baseline rather than absolute levels might have resulted in different findings.

An additional general limitation is that the follow-up period was only 4 weeks. It is possible that treatment effects will wear off after a few months.

Since we included medicated participants, our psychophysiological data may have been somewhat compromised. We minimized pharmacological effects by only accepting patients who reported stable doses and by excluding cardiovascular and electrodermal data from patients saying that they took drugs with known effects on these systems. Nevertheless, we cannot be certain that all such effects were eliminated.

Our criterion for occurrence of a panic attack may have been too conservative, accounting for the lack of differences between groups. Often studies used a more complicated criterion to define panic attacks, such as experiencing at least four physical symptoms in addition to high anxiety (e.g., van den Hout, Marcel A., van der Molen, Griez, Lousberg, & Nansen, 1987). However, we took the standpoint of Holt & Andrews (1989b) that relying on the number of symptoms is misleading since physical sensations and anxiety during challenges are also experienced by non-anxious people. Ultimately, what is called a panic attacks is subjective.

Finally, we need to point out that although overall we had a sufficient number of patients, when they were divided into 3 groups, numbers per treatment were fairly low. Sample sizes were reduced further for the psychophysiological analyses since we had to exclude subjects that did not comply with the instructions. There is reason to believe that a bigger sample may have resulted in more group differences. Furthermore, we were unable to conduct meaningful correlation analyses between the psychological and physiological measures due to the small sample sizes.

Implications and Future Directions

Our investigation of breathing abnormalities in PD and patients suffering from episodic anxiety attacks without a history of PD resulted in mixed findings. We replicated baseline abnormalities in PD but did not find an exaggerated response to voluntary hypo-

and hyperventilation compared to NAC. Episodic Anxiety patients showed abnormalities neither at baseline nor in reaction to the respiratory challenges. However, both patient groups benefited from the breathing therapies. Hypocapnic and hypercapnic treatment were equivalent in their outcome, which challenges the idea that a change of breathing was the main working mechanism. Improvement can rather be attributed to factors unrelated to the direct manipulation of pCO_2. However, both treatment conditions were comparable on important variables such as duration of therapy, patient-therapist interaction, direction of attention to bodily sensations, and regularizing and slowing down breathing with use of a capnometer. Future trials of breathing therapies should be designed that keep the pCO_2 level constant but manipulate other variables related and unrelated to breathing.

In terms of laboratory tests, more work is needed to disentangle specific factors influencing the results such as duration of breathing manipulation, target pCO_2 levels, breathing frequency, and the use of pacing aids. Furthermore, paused breathing may be more efficient in raising one's CO_2 than the method we taught patients. In another study, conducted at the same time as the one reported here, we found that healthy subjects were able to raise their pCO_2 about 10 mm Hg by quick inhalation, paused breathing for 18 seconds, and quick exhalation (Wollburg, Roth, & Kim, under review). This breathing pattern may be a better way to raise CO_2 than, for example, gas mixtures, which have many psychological and physiological limitations.

Unfortunately, we were unable to run follow-up analyses on the subgroups of PD that have been suggested in the literature. Needless to say, it is important to know whether a respiratory subtype of PD would benefit more from the BT than other subtypes. In terms of our second patient group, the EA patients, future trials with more stringent inclusion criteria need to be run. Although unlikely to have influenced our results, patients with OCD should be evaluated as a separate group in future studies since they did not show respiratory abnormalities in past studies. Hence, they may dilute the common respiratory characteristics of other EA subgroups.

Our short-term breathing therapies were effective in a substantial portion of patients. In the future, investigation of long-term outcome and direct comparison with standard CBT treatments would be useful to assess their clinical value more thoroughly. We hope that our breathing therapies will turn out to be long-term efficacious treatments for PD and other patients suffering from anxiety attacks, which may equal or surpass existing pharmacological and cognitive treatments.

REFERENCES

Abelson, J. L., Nesse, R. M., Weg, J. G., & Curtis, G. C. (1996). Respiratory psychophysiology and anxiety: Cognitive intervention in the doxapram model of panic. *Psychosomatic Medicine, 58*, 302-313.

Abelson, J. L., Weg, J. G., Nesse, R. M., & Curtis, G. C. (2001). Persistent respiratory irregularity in patients with panic disorder. *Biological Psychiatry, 49*, 588-595.

Abrams, K., Rassovsky, Y., & Kushner, M. G. (2006). Evidence for respiratory and nonrespiratory subtypes in panic disorder. *Depression and Anxiety, 23*, 474-481.

Alpers, G. W., Wilhelm, F. H., & Roth, W. T. (2005). Psychophysiological assessment during exposure in driving phobic patients. *Journal of Abnormal Psychology, 114*(1), 126-139.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington, DC.

Antony, M. M., Brown, T. A., & Barlow, D. H. (1997). Response to hyperventilation and 5.5% CO2 inhalation of subjects with types of specific phobia, panic disorder, or no mental disorder. *American Journal of Psychiatry, 154*(8), 1089-1095.

Asmundson, G. J. G., Norton, G. R., Wilson, K. G., & Sandler, L. S. (1994). Subjective symptoms and cardiac reactivity to brief hyperventilation in individuals with high anxiety sensitivity. *Behaviour Research and Therapy, 32*(2), 237-241.

Asmundson, G. J. G., & Stein, M. B. (1994). Triggering the false suffocation alarm in panic disorder patients by using a voluntary breath-holding procedure. *American Journal of Psychiatry, 151*(2), 264-266.

Bagiella, E., Sloan, R. P., & Heitjan, D. F. (2000). Mixed-effects models in psychophysiology. *Psychophysiology, 37*, 13-20.

Ball, S., & Shekkar, A. (1997). Basilar artery response to hyperventilation in panic disorder. *American Journal of Psychiatry, 154*, 1603-1604.

Barlow, D. H. (1988). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. New York: Guilford Press.

Barlow, D. H. (1991). The nature of anxiety: Anxiety, depression, and emotional disorders. In R. M. Rapee & D. H. Barlow (Eds.), *Chronic anxiety, generalized anxiety disorder, and mixed anxiety-depression* (pp. 1-28). New York: Guilford Press.

Barlow, D. H. (2002). *Anxiety and its Disorders: The nature and treatment of anxiety and panic* (2nd ed.). New York: Guilford Press.

Bass, C., Lelliott, P., & Marks, I. (1989). Fear talk versus voluntary hyperventilation in agoraphobics and normals: a controlled study. *Psychological Medicine, 19*, 669-676.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 41*, 561-571.

Biber, B., & Alkin, T. (1999). Panic disorder subtypes: Differential responses to CO2 challenge. *American Journal of Psychiatry, 156*(5), 739-744.

Bonn, J. A., Readhead, C. P., & Timmons, B. H. (1984). Enhanced adaptive behavioral response in agoraphobic patients pretreated with breathing retraining. *Lancet, 2*, 665-669.

Briggs, A. C., Stretch, D. D., & Brandon, S. (1993). Subtyping of panic disorder by symptom profile. *British Journal of Psychiatry, 163*, 201-209.

Bystritsky, A., Craske, M. G., Maidenberg, E., Vapnik, T., & Shapiro, D. (2000). Autonomic reactivity of panic patients during a CO2 inhalation procedure. *Depression and Anxiety, 11*, 15-26.

Bystritsky, A., & Shapiro, C. M. (1992). Continuous physiological changes and subjective reports in panic patients: A preliminary methodological report. *Biological Psychiatry, 32*, 766-777.

Caldirola, D., Perna, G., Arancio, C., Bertani, A., & Bellodi, L. (1997). The 35% CO2 challenge test in patients with social phobia. *Psychiatry Research, 71*, 41-48.

Carter, M. M., Suchday, S., & Gore, K. L. (2001). The utility of the ASI factors in predicting response to voluntary hyperventilation among nonclinical participants. *Journal of Anxiety Disorders, 15*, 217-230.

Chambless, D. L., Caputo, G. C., Jasin, S. E., Gracely, E. J., & Williams, C. (1985). The Mobility Inventory for Agoraphobia. *Behavior Research and Therapy, 23*(1), 35-44.

Clark, C. R. (1986). A cognitive approach to panic. *Behaviour Research and Therapy, 24*(4), 461-470.

Clark, C. R., Salkovskis, P. M., & Chalkley, A. J. (1985). Respiratory control as a treatment for panic attacks. *Journal of Behaviour Therapy and Experimental Psychiatry, 16*(1), 23-30.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

Cowley, D. S., & Roy-Byrne, P. P. (1987). Hyperventilation and panic disorder. *The American Journal of Medicine, 83*, 929-937.

Cox, B. J., Borger, S. C., & Enns, M. W. (1999). Anxiety sensitivity and emotional disorders: Psychometric studies and their theoretical implications. In S. Taylor (Ed.), *Anxiety sensitivity: Theory, research, and the treatment of the fear of anxiety*. Mahwah, NJ: Erlbaum.

Craske, M. G., Rowe, M., Lewin, M., & Noriega-Dimitri, R. (1997). Interoceptive exposure versus breathing retraining within cognitive-behavioural therapy for panic disorder with agoraphobia. *British Journal of Clinical Psychology, 36*, 85-99.

de Beurs, E., Garssen, B., Buikhuisen, M., Lange, A., van Balkom, A., & van Dyck, R. (1994). Continuous monitoring of panic. *Acta Psychiatrica Scandinavica, 90*, 38-43.

de Ruiter, C., Ruken, H., Garssen, B., & Kraaimaat, F. (1989). Breathing retraining, exposure and a combination of both, in the treatment of panic disorder with agoraphobia. *Behaviour Research and Therapy, 27*(6), 647-655.

Ehlers, A., Margraf, J., Roth, W. T., Taylor, C. B., Maddock, R. J., Sheikh, J., et al. (1986). Lactate infusions and panic attacks: do patients and controls respond differently? *Psychiatry Research, 17*, 295-308.

Feldner, M. T., Zvolensky, M. J., Stickle, T. R., Bonn-Miller, M. O., & Leen-Feldner, E. W. (2006). Anxiety sensitivity - physical concerns as a moderator of the emotional consequences of emotion suppression during biological challenge: an

experimental test using individual growth curve analysis. *Behavior Research and Therapy, 44*, 249-272.

First, M. B., Gibbon, M., Spitzer, R. L., & Williams, J. B. (2002). Structured Clinical Interview For DSM-IV Disorders - Research Version.

Fried, R., & Grimaldi, J. (1993). *The psychology and physiology of breathing in behavioral medicine, clinical psychology, and psychiatry*. New York: Plenum Press.

Friedman, S. D., Mathis, C. M., Hayes, C., Renshaw, P., & Dager, S. R. (2006). Brain pH Response to Hyperventilation in Panic Disorder: Preliminary Evidence for Altered Acid-Base Regulation. *American Journal of Psychiatry, 163*(4), 710-715.

Garssen, B., Buikhuisen, M., & van Dyck, R. (1996). Hyperventilation and panic attacks. *American Journal of Psychiatry, 153*, 513-518.

Goetz, R., Klein, D. F., Gully, R., Kahn, J., Liebowitz, M. R., Fyer, A. J., et al. (1993). Panic attacks during placebo procedures in the laboratory: physiology and symptomatology. *Archives of General Psychiatry, 50*, 280-285.

Gorman, J. M., Askanazi, J., Liebowitz, M. R., Fyer, A. J., Stein, J., Kinney, J. M., et al. (1984). Response to hyperventilation in a group of patients with panic disorder. *American Journal of Psychiatry, 141*, 857-861.

Gorman, J. M., Fyer, A. J., Ross, D. C., Cohen, B. S., Martinez, J. M., Liebowitz, M. R., et al. (1985). Normalization of venous pH, pCO2, and bicarbonate levels after blockade of panic attacks. *Psychiatry Research, 14*, 57-65.

Gorman, J. M., Fyer, M. R., Goetz, R. R., Askanazi, J., Liebowitz, M. R., Fyer, A. J., et al. (1988). Ventilatory physiology of patients with panic disorder. *Archives of General Psychiatry, 45*, 31-39.

Gorman, J. M., Kent, J. M., Martinez, J. M., Browne, S. T., Coplan, J. D., & Papp, L. A. (2001). Physiological changes during carbon dioxide inhalation in patients with panic disorder, major depression, and premenstrual dysphoric disorder: evidence for a central fear mechanism. *Archives of General Psychiatry, 58*, 125-131.

Gorman, J. M., Martinez, J. M., Coplan, J. D., Kent, J. M., & Kleber, M. (2004). The effect of successful treatment on the emotional and physiological response to carbon dioxide inhalation in patients with panic disorder. *Biological Psychiatry, 56*, 862-867.

Gorman, J. M., Papp, L. A., Coplan, J. D., Martinez, J. M., Lennon, R. N., Goetz, R. R., et al. (1994). Anxiogenic effects of CO-sub-2 and hyperventilation in patients with panic disorder. *American Journal of Psychiatry, 151*, 547-553.

Gorman, J. M., Papp, L. A., Martinez, J. M., Goetz, R. R., Hollander, E., Liebowitz, M. R., et al. (1990). High-dose carbon dioxide challenge test in anxiety disorder patients. *Biological Psychiatry, 28*, 743-757.

Griez, E., de Loof, C., Pols, H., Zandbergen, J., & Lousberg, H. (1990). Specific sensitivity of patients with panic attacks to carbon dioxide inhalation. *Psychiatry Research, 31*, 193-199.

Griez, E., & Schruers, K. (1998). Experimental pathophysiology of panic. *Journal of Psychosomatic Research, 45*(6), 493-503.

Griez, E., & van den Hout, M. A. (1987). Acid-base balance in real life panic. *Journal of Affective Disorders, 12*, 263-266.

Grossman, P., de Swart, J. C. G., & Defares, P. B. (1985). A controlled study of a breathing therapy for treatment of hyperventilation syndrome. *Journal of Psychosomatic Research, 29*(1), 49-58.

Hegel, M. T., & Ferguson, R. J. (1997). Psychophysiological assessment of respiratory function in panic disorder: Evidence for a hyperventilation subtype. *Psychosomatic Medicine, 59*, 224-230.

Hibbert, G. A., & Chan, M. (1989). Respiratory control: its contribution to the treatment of panic attacks. *British Journal of Psychiatry, 154*, 232-236.

Hibbert, G. A., & Pilsbury, D. (1988). Hyperventilation in panic attacks. *British Journal of Psychiatry, 153*, 76-80.

Hibbert, G. A., & Pilsbury, D. (1989). Hyperventilation: Is it a cause of panic attacks? *British Journal of Psychiatry, 155*, 805-809.

Hoehn-Saric, R., McLeod, D. R., Funderburk, F., & Kowalski, P. (2004). Somatic symptoms and physiologic responses in generalized anxiety disorder and panic disorder. *Archives of General Psychiatry, 61*, 913-921.

Holloway, W., & McNally, R. J. (1987). Effects of Anxiety Sensitivity on the Response to Hyperventilation. *Journal of Abnormal Psychology, 96*(4), 330-334.

Holt, P. E., & Andrews, G. (1989a). Hyperventilation an anxiety in panic disorder, social phobia, GAD and normal controls. *Behaviour Research and Therapy, 27*(4), 453-460.

Holt, P. E., & Andrews, G. (1989b). Provocation of panic: Three elements of the panic reaction in four anxiety disorders. *Behaviour Research and Therapy, 27*(3), 253-261.

Hornsveld, H., Garssen, B., & van Spiegel, P. I. (1995). Voluntary hyperventilation: the influence of duration and depth on the development of symptoms. *Biological Psychology, 40*, 299-312.

Katzman, M. A., Struzik, L., Vijay, N., Coonerty-Femiano, A., Mahamed, S., & Duffin, J. (2002). Central and peripheral chemoreflexes in panic disorder. *Psychiatry Research, 15*(1-2), 181-192.

Kent, J. M., Papp, L. A., Martinez, J. M., Browne, S. T., Coplan, J. D., Klein, D. F., et al. (2001). Specificity of panic response to CO2 inhalation in panic disorder: A comparison with major depression and premenstrual dysphoric disorder. *American Journal of Psychiatry, 158*, 58-67.

Kerr, W. M. J., Dalton, J. W., & Gliebe, P. A. (1937). Some physical phenomena associated with the anxiety states and their relation to hyperventilation. *Annals of Internal Medicine, 11*, 961-992.

Klein, D. F. (1993). False suffocation alarms, spontaneous panics, and related conditions; An integrative hypothesis. *Archives of General Psychiatry, 50*, 306-318.

Klein, D. F. (1994). Testing the suffocation false alarm theory of panic disorder. *Anxiety, 1*, 1-7.

Klein, D. F., & Klein, H. M. (1989). The nosology, genetics, and theory of spontaneous panic and phobia. In P. Tyrer (Ed.), *Psychopharmacology of anxiety* (pp. 163-195). New York: Oxford University Press.

Kroeze, S., & van den Hout, M. A. (1998). No superior perception of hyperventilatory sensations in panic disorder. *Behaviour Research and Therapy, 36*, 285-295.

Ley, R. (1985). Blood, breath, and fears: A hyperventilation theory of panic attacks and agoraphobia. *Clinical Psychology Review, 5*, 271-285.

Ley, R. (1987). Panic Disorder: A Hyperventilation Interpretation. In L. Michaelson & M. Ascher (Eds.), *Cognitive-behavioral assessment and treatment of anxiety disorders* (pp. 191-212). New York: Guilford Press.

Ley, R. (1989). Dyspneic-fear and catastrophic cognitions in hyperventilatory panic attacks. *Behaviour Research and Therapy, 27*(5), 549-554.

Ley, R. (1992). The many faces of pan: Psychological and physiological differences among three types of panic attacks. *Behaviour Research and Therapy, 30*(4), 347-357.

Lousberg, H., Griez, E., & van den Hout, M. A. (1988). Carbon dioxide chemosensitivity. *Acta Psychiatrica Scandinavica 77*, 214-218.

Lynch, P., Bakal, D., Whitelaw, W., Fung, T., & Rose, L. (1992). Agoraphobic avoidance and panic frequency as predictors of laboratory induced panic reactions. *Behaviour Research and Therapy 30*(6), 591-596.

Maddock, R. J., & Carter, C. S. (1991). Hyperventilation-induced panic attacks in panic disorder with agoraphobia. *Biological Psychiatry, 29*, 843-854.

Margraf, J., Taylor, C. B., Ehlers, A., Roth, W. T., & Agras, W. S. (1987). Panic attacks in the natural environment. *Journal of Nervous and Mental Disease, 175*, 558-565.

Martinez, J. M., Coplan, J. D., Brown, E. B., Goetz, R., Welkowitz, L., Papp, L. A., et al. (1998). Hemodynamic response to respiratory challenges in panic disorder. *Journal of Psychosomatic Research, 44*(1), 153-161.

Martinez, J. M., Kent, J. M., Coplan, J. D., Browne, S. T., Papp, L. A., Sullivan, G. M., et al. (2001). Respiratory variability in panic disorder. *Depression and Anxiety, 14*, 232-237.

Martinez, J. M., Papp, L. A., Coplan, J. D., Anderson, D. E., Mueller, C. M., Klein, D. F., et al. (1996). Ambulatory monitoring of respiration in anxiety. *Anxiety, 2*, 296-302.

Meuret, A. E., White, K. S., Ritz, T., Roth, W. T., Hofmann, S. G., & Brown, T. A. (2006). Panic attack symptom dimensions and their relationship to illness characteristics in panic disorder. *Journal of Psychiatric Research, 40*, 520-527.

Meuret, A. E., Wilhelm, F. H., Ritz, T., & Roth, W. T. (2003). Breathing training for treating panic disorder. Useful intervention or impediment? *Behaviour Modification, 27*, 1-24.

Meuret, A. E., Wilhelm, F. H., Ritz, T., & Roth, W. T. (in press). Feedback of end-tidal pCO2 as a therapeutic approach for panic disorder. *Journal of Psychiatric Research*.

Meuret, A. E., Wilhelm, F. H., & Roth, W. T. (2001). Respiratory biofeedback-assisted therapy in panic disorder. *Behaviour Modification, 25*, 584-605.

Meuret, A. E., Wilhelm, F. H., & Roth, W. T. (2004). Respiratory feedback for treating panic disorder. *Journal of Clinical Psychology, 60*(2), 197-207.

Munjack, D. J., Brown, R. A., & McDowell, D. E. (1993). Existence of hyperventilation in panic disorder with and without agoraphobia, GAD, and normals: Implications for the cognitive theory of panic. *Journal of Anxiety Disorders, 7*, 37-48.

Nardi, A. E., Nascimento, I., Valença, A. M., Lopes, F. L., Mezzasalma, M. A., & Zin, W. A. (2003). Panic disorder in a breath-holding challenge test_A simple tool for a better diagnosis. *Arquivos de Neuro-Psiquiatria, 61*(3), 718-722.

Nardi, A. E., Valença, A. M., Lopes, F. L., Nascimento, I., Veras, A. B., Freire, R. C., et al. (2006). Psychopathological profile of 35% CO2 challenge test-induced panic attacks: A comparison with spontaneous panic attacks. *Comprehensive Psychiatry, 47*, 209-214.

Nardi, A. E., Valenca, A. M., Nascimento, I., & Zin, W. A. (2001). Hyperventilation challenge test in panic disorder and depression with panic attacks. *Psychiatry Research, 105*, 57-65.

Nardi, A. E., Valenca, A. M., Nascimento, I., & Zin, W. A. (2002). Panic disorder and obsessive compulsive disorder in a hyperventilation challenge test. *Journal of Affective Disorders, 68*, 335-340.

Papp, L. A., Klein, D. F., & Gorman, J. M. (1993). Carbon dioxide hypersensitivity, hyperventilation, and panic disorder *American Journal of Psychiatry, 150*(8), 1149-1156.

Papp, L. A., Klein, D. F., Martinez, J. M., Schneier, F., Cole, R., Jordan, F., et al. (1993). Diagnostic and substance specificity of carbon-dioxide-induced panic. *American Journal of Psychiatry, 150*(2), 250-257.

Papp, L. A., Martinez, J. M., Klein, D. F., Coplan, J. D., & Gorman, J. M. (1995). Rebreathing tests in panic disorder. *Biological Psychiatry, 38*, 240-245.

Papp, L. A., Martinez, J. M., Klein, D. F., Coplan, J. D., Norman, R. G., Cole, R., et al. (1997). Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. *American Journal of Psychiatry, 154:11*, 1557-1565.

Perna, G., Battaglia, M., Garberi, A., Arancio, C., Bertani, A., & Bellodi, L. (1994). Carbon Dioxide/Oxygen challenge test in panic disorder. *Psychiatry Research, 52*, 159-171.

Perna, G., Gabriele, A., Caldirola, D., & Bellodi, L. (1995). Hypersensitivity to inhalation of carbon dioxide and panic attacks. *Psychiatry Research, 57*, 267-273.

Peterson, R. A., & Reiss, S. (1993). *Anxiety Sensitivity Index Revised test manual*. Worthington, OH: IDS Publishing Corporation.

Rapee, R. M. (1986). Differential response to hyperventilation in panic disorder and generalized anxiety disorder. *Journal of Abnormal Psychology, 95*, 24-28.

Rapee, R. M. (1990). Psychological mechanisms underlying the response to biological challenge procedures in panic disorder. In N. McNaughton & G. Andrews (Eds.), *Anxiety* (pp. 75-81). Dunedin, New Zealand: University of Otago Press.

Rapee, R. M., Brown, T. A., Antony, M. M., & Barlow, D. H. (1992). Response to hyperventilation and inhalation of 5.5% carbon dioxide-enriched air across the DSM-lll anxiety disorders. *Journal of Abnormal Psychology, 101*, 538-552.

Rapee, R. M., & Medoro, L. (1994). Fear of Physical Sensations and Trait Anxiety as Mediators of te Response to Hyperventilation in Nonclinical Subjects. *Journal of Abnormal Psychology, 103*(4), 693-699.

Rassovsky, Y., Abrams, K., & Kushner, M. G. (2006). Suffocation and respiratory responses to carbon dioxide and breath holding challenges in individuals with panic disorder. *Journal of Psychosomatic Research, 60*, 291-298.

Reiss, S., & McNally, R. J. (1985). Expectancy model of fear. In S. Reiss & R. R. Bootzin (Eds.), *Theoretical issues in behavior therapy* (pp. 107-121). San Diego: Academic Press.

Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy, 24*(1), 1-8.

Roth, W. T., Margraf, J., Ehlers, A., Taylor, C. B., Maddock, R. J., Davies, S. O., et al. (1992). Stress test reactivity in panic disorder. *Archives if General Psychiatry, 49*, 301-310.

Roth, W. T., Wilhelm, F. H., & Trabert, W. (1998). Autonomic instability during relaxation in panic disorder. *Psychiatry Research, 1998*, 155-164.

Rottenberg, J., Wilhelm, F. H., Gross, J., & Gotlib, I. (2002). Respiratory sinus arrthythmia as a predictor of outcome in major depressive disorder. *Journal of Affective Disorders, 71*, 265-272.

Salkovskis, P. M., Jones, D. R., & Clark, D. M. (1986). Respiratory control in the treatment of panic attacks: Replication and extension with concurrent measurement of behaviour and pCO2. *British Journal of Psychiatry, 148*, 526-532.

Salkovskis, P. M., Warwick, H. M. C., Clark, C. R., & Wessels, D. J. (1986). A demonstration of acute hyperventilation during naturally occurring panic attacks. *Behaviour Research and Therapy, 24*(1), 91-94.

Sanderson, W. C., Rapee, R. M., & Barlow, D. H. (1989). The influence of an illusion of control on panic attacks induced via inhalation of 5.5% carbon dioxide-enriched air. *Archives of General Psychiatry, 46*, 157-162.

Schmidt, N. B., Forsyth, J. P., Santiago, H., & Trakowski, J. (2002). Classification of panic attack subtypes in patients and normal controls in response to biological challenge: implications for assessment and treatment. *Journal of Anxiety Disorders, 16*(6), 625-638.

Schmidt, N. B., Lerew, D. R., & Jackson, R. J. (1997). The role of anxiety sensitivity in the pathogenesis of panic: Prospective evaluation of spontaneous panic attacks during acute stress. *Journal of Abnormal Psychology, 106*(3), 355-364.

Schmidt, N. B., & Mallott, M. (2006). Evaluating anxiety sensitivity and other fundamental sensitivities predicting anxiety symptoms and fearful responding to a biological challenge. *Behavior Research and Therapy, 44*(11), 1681-1688.

Schmidt, N. B., Telch, M. J., & Jaimez, T. L. (1996). Biological challenge manipulation of PCO2 levels: A test of Klein´s (1993) suffocation alarm theory of panic. *Journal of Abnormal Psychology, 105*(3), 446-454.

Schmidt, N. B., Woolaway-Bickel, K., Trakowski, J., Santiago, H., Storey, J., Koselka, M., et al. (2000). Dismantling cognitive-behavioral treatment for panic disorder: Questioning the utility of breathing retraining. *Journal of Consulting and Clinical Psychology, 68*(3), 417-424.

Shear, M. K., Brown, T. A., Barlow, D. H., Sholomskas, D., Woods, S. W., Gorman, J. M., et al. (1997). Multicenter Collaborative Panic Disorder Severity Scale. *American Journal of Psychiatry, 154*, 1571-1575.

Shear, M. K., Polan, J. J., Harshfield, G., Pickering, T., Mann, J. J., Frances, A., et al. (1992). Ambulatory monitoring of blood pressure and heart rate in panic patients. *Journal of Anxiety Disorders, 6*, 213-221.

Sheehan, D. V., Harnett-Sheehan, K., & Raj, B. A. (1996). The measurement of disability. *International Clinical Psychopharmacology, 11*(suppl. 3), 89-95.

Sloan, E. P., Natarajan, M., Baker, B., Dorian, P., Mironov, D., Barr, A., et al. (1999). Nocturnal and daytime panic attacks: Comparison of sleep architecture, heart rate variability, and response to sodium lactate challenge. *Biological Psychiatry, 45*, 1313-1320.

Stein, M. B., Millar, T. W., Larsen, D. K., & Kryger, M. H. (1995). Irregular breathing during sleep in patients with panic disorder. *American Journal of Psychiatry, 152*(8), 1168-1173.

Sturges, L. V., Goetsch, V. L., Ridley, J., & Whittal, M. (1998). Anxiety sensitivity and response to hyperventilation challenge: physiologic arousal, interoceptive acuity, and subjective distress. *Journal of Anxiety Disorders, 12*(2), 103-115.

Sullivan, G. M., Kent, J. M., Kleber, M., Martinez, J. M., Yeragani, V. K., & Gorman, J. M. (2004). Effects of hyperventilation on heart rate and QT variability in panic disorder pre- and post-treatment. *Psychiatry Research, 125*, 29-39.

Taylor, S., Koch, W., McNally, R. J., & Crockett, D. J. (1992). Conceptualisation of anxiety sensitivity. *Psychological Assessment, 4*, 245-250.

Thyer, B. A., Papsdorf, J. D., & Wright, P. (1984). Physiological and psychological effects of acute intentional hyperventilation. *Behaviour Research and Therapy, 22*(5), 587-590.

Valença, A. M., Nardi, A. E., Nascimento, I., Zin, W. A., & Versiani, M. (2002a). Carbon dioxide test as an additional clinical measure of treatment response in panic disorder. *Arquivos de Neuro-Psiquiatria, 60*(2), 358-361.

Valença, A. M., Nardi, A. E., Nascimento, I., Zin, W. A., & Versiani, M. (2002b). Respiratory panic disorder subtype and sensitivity to the carbon dioxide challenge test. *Brazilian Journal of Medical and Biological Research, 35*, 783-788.

van den Hout, M. A., Hoekstra, R., Arntz, A., Christianse, M., Ranschaert, W., & Schouten, E. (1992). Hyperventilation is not diagnostically specific to panic patients. *Psychosomatic Medicine, 53*, 182-191.

van den Hout, M. A., van der Molen, G. M., Griez, E., Lousberg, H., & Nansen, A. (1987). Reduction of CO2-induced anxiety in patients with panic attacks after repeated CO2 exposure. *American Journal of Psychiatry, 144*(6), 788-791.

Verburg, K., Griez, E., Meijer, J., & Pols, H. (1995). Discrimination between panic disorder and generalized anxiety disorder by 35% carbon dioxide challenge. *American Journal of Psychiatry, 152*(7), 1081-1083.

Whittal, M. L., & Goetsch, V. L. (1995). Physiological, subjective and behavioral responses to hyperventilation in clinical and infrequent panic. *Behaviour Research and Therapy, 33*(4), 415-422.

Wilhelm, F. H., Gerlach, A. L., & Roth, W. T. (2001). Slow recovery from voluntary hyperventilation in panic disorder. *Psychosomatic Medicine, 63*, 638-649.

Wilhelm, F. H., & Roth, W. T. (1998). Taking the laboratory to the skies: Ambulatory assessment of self-report, autonomic, and respiratory responses in flying phobia. *Psychophysiology, 35*, 596-606.

Wilhelm, F. H., Trabert, W., & Roth, W. T. (2001a). Characteristics of sighing in panic disorder. *Biological Psychiatry, 49*, 606-614.

Wilhelm, F. H., Trabert, W., & Roth, W. T. (2001b). Physiologic instability in panic disorder and generalized anxiety disorder. *Biological Psychiatry, 49*(7), 596-605.

Wollburg, E., Kim, S., Conrad, A., & Roth, W. T. (2007). Physiological Evaluation of psychological treatments for anxiety. *Expert Review of Neurotherapeutics, 7*(2), 129-141.

Wollburg, E., Roth, W. T., Conrad, A., Meuret, A. E., & Kim, S. (in press). Psychophysiological reactions to two levels of voluntary hyperventilation in panic disorder. *Journal of Anxiety Disorders*.

Woods, S. W., Charney, D. S., Goodman, W. K., & Heninger, G. R. (1988). Carbon dioxide-induced anxiety: Behavioral, physiologic, and biochemical effects of carbon dioxide in patients with panic disorder and healthy subjects. *Archives of General Psychiatry, 45*, 43-52.

Woods, S. W., Charney, D. S., Loke, J., Goodman, W. K., Redmond, D. E., & Heninger, G. R. (1986). Carbon dioxide sensitivity in panic anxiety. *Archives of General Psychiatry, 43*, 900-909.

Zandbergen, J., Lousberg, H., Pols, H., de Loof, C., & Griez, E. (1990). Hypercarbia versus hypocarbia in panic disorder. *Journal of Affective Disorders, 18*(2), 75-81.

Zandbergen, J., van Aalst, V., de Loof, C., Pols, H., & Griez, E. (1993). No chronic hyperventilation in panic disorder patients. *Psychiatry Research, 47*(1), 1-6.