Challenging Anxiety: A Focus on the Specificity of Respiratory Symptoms

M.A. Van Duinen, V. Niccolai, and E.J.L. Griez

Contents

Abstract Physiological symptoms are characteristic features of anxiety states. Presumably, specific psychophysiological profiles differentiate between anxiety disorders, which would offer potential for diagnostic purposes. Abundant evidence points to a causal relationship between panic disorder and instability of respiratory regulation. However, the specificity of most measures that indicate aberrant functioning of the respiratory system in PD can be questioned. Possibly, the traditional measures of respiratory functioning are too restricted. The underlying respiratory vulnerability in PD seems to constitute a subtle, unstable trait, which calls for more

M.A. Van Duinen (✉) and E.J.L. Griez
Psychiatry & Neuropsychology, Maastricht University, The Netherlands
V. Niccolai
Institute of Experimental Psychology II, Heinrich-Heine University of Düsseldorf, Germany

M.B. Stein and T. Steckler (eds.), *Behavioral Neurobiology of Anxiety and Its Treatment,* 229
Current Topics in Behavioral Neurosciences 2, DOI 10.1007/7854_2009_33,

sensitive and sophisticated measures of respiratory variability and chaos. To increase the probability of finding parameters with diagnostic specificity, the application of disorder specific challenge paradigms is recommended.

Keywords Anxiety · Respiration · Panic disorder · Psychophysiology

1 Introduction

The presumably, primal response during the active state of anxiety disorders, shows many resemblances with a normal defensive response. Autonomic changes described for the classic stress response include a wide range of physiological systems including the respiratory and cardiovascular systems. It is conceivable that specific anxiety disorders show characteristic psychophysiological profiles. In case the physiological profile of different anxiety disorders could serve as an objective discriminator, this would not only be of scientific interest, but could even offer potential for diagnostic purposes.

The provocation of anxiety symptoms under standardized conditions has proven to contribute to a better understanding of anxiety disorders, both from a behavioral and biological point of view. Especially in social phobia and panic disorder (PD), well-defined paradigms are available that reliably provoke specific core phenomena in affected persons. However, for other anxiety disorders, specific, standardized challenges inducing the relevant affective state are described to a lesser extent.

Generally, we can state that there are two types of anxiety provocation. Exposure to exteroceptive stimuli, that is exposing patients to feared situations or stimuli, or interoceptive exposure in which bodily sensations or disorder-related thoughts are evoked. One way to evoke bodily sensation is by means of chemical stimulation. Over the years, quite some compounds have been claimed to provoke instances of clinical anxiety. However, most of these models have been criticized for their lack of specificity. In general, biochemical manipulations induce merely a state of general anxiety rather than symptoms resembling an affective state relevant to the anxiety disorder under study.

Compared to other anxiety disorders, the induction of specific symptoms by means of chemical stimulation is best described in PD. It might not come as a surprise that PD is particularly suitable for chemical symptom induction. The unexpected attacks with clear bodily sensations are not induced by an external stimulus but rather appear from an internal distortion.

A noteworthy similarity among most of the pharmacological agents that have been proposed as specific panicogenics, is the ability to exert a strong influence on respiration (Calverley et al. 1983; Liebowitz et al. 1984; Charney et al. 1985; Griez et al. 1987; Bradwejn et al. 1990). Moreover, respiratory symptoms represent a category that is present during the core phenomenon of PD – the panic attack.

Consequently, studies focusing on possible dysregulated respiratory patterns in this particular disorder have strongly increased in the past few decades. Evidence from these studies show that PD subjects are particularly sensitive to respiratory challenges. Especially the respiratory subgroup, characterized by prominent respiratory symptoms during panic attacks, seems to be associated with an increased sensitivity to respiratory challenges (Maddock and Carter 1991; Valenca et al. 2002). In addition, this subgroup might present a distinct endophenotype characterized by an earlier onset of the disorder, more frequent spontaneous panic attacks, a higher familial prevalence of PD, more previous depressive episodes, and a different profile with regard to pharmacological responsiveness (Briggs et al. 1993; Nardi et al. 2006).

The abundant attention for respiration within the field of PD cannot be neglected. However, for other anxiety disorders, respiratory symptoms have not been the primary focus. Although sympathetic activity in general has been studied, respiratory symptoms were often neglected. Is it because of the evident presence of respiratory symptoms during panic attacks that respiratory symptoms are principally reported in studies on PD, or could affected respiration also be an endophenotypic trait of other anxiety disorders? In this chapter, we focus on the specificity of respiratory symptoms for PD and we discuss the peculiarity of the relationship between respiratory symptoms and different anxiety disorders.

2 Panic-Respiration or Anxiety-Respiration Link?

Respiratory symptoms, such as hyperventilation, dyspnea, and a feeling of choking or breathlessness are commonly described as prominent symptoms of a panic attack. With regard to other anxiety disorders, only for generalized anxiety disorder (GAD) a respiratory symptom has been explicitly mentioned in the DSM (APA 1994).

Hyperventilation, in particular, is consistently observed during laboratory-induced panic attacks (Gorman et al. 1986; Papp et al. 1989). Basically, hyperventilation implies breathing in excess of metabolic need, thus lowering arterial pCO_2 and resulting in increased pH. Although a fundamental role for hyperventilation in triggering panic was proposed previously (Ley 1985), it has been demonstrated that hyperventilation is not a causal mechanism in the initiation of panic. It rather constitutes one of the many symptoms that can emerge during an attack (Hornsveld and Garssen 1997).

A second main respiratory symptom in the spectrum of PD is dyspnea, defined as "breathing discomfort consisting of qualitatively distinct sensations that vary in intensity". In an early report of Rapee et al. (1992b), symptom profiles based on DSM-III-R panic symptoms were compared between PD patients and subjects suffering from other anxiety disorders (social phobia, specific phobia, and obsessive-compulsive disorder). Subjects were retrospectively questioned on the occurrence of these specific symptoms during a panic attack or a cued phobic or OCD response.

All panic symptoms were reported to occur during attacks in both groups, with a higher prevalence in the PD group for all items. Seven out of fourteen panic symptoms were reported significantly more often by PD patients among which dyspnea.

Although dyspnea seems to indicate pulmonary obstruction, the occurrence of dyspnea does not seem to be related to structural changes in the cardiopulmonary system. On the contrary, severe structural change is not required for the experience of dyspnea (Dudley et al. 1968). Patients with so-called medically unexplained dyspnea reported more intense dyspnea than patients with organic lung diseases. As a symptom, dyspnea depends for its identification on the subjective judgment of the patient. No objective tests (e.g., blood gas or ventilatory abnormalities) are available to date. However, Han et al. (2004) showed that subjects with medically unexplained dyspnea could be distinguished from subjects with organic dyspnea by using a small set of psychological and physiological measures, including PaO_2 and forced expiratory volume in 1 s. Furthermore, one-third of these patients met the criteria for PD.

In addition to the characteristic occurrence of respiratory symptoms during panic attacks, an increased prevalence of respiratory diseases has been reported in PD patients as compared to both healthy control subjects and patients with other anxiety disorders (Zandbergen et al. 1991). Vice versa, the lifetime prevalence of PD in patients with asthma is higher than expected in comparison with epidemiologic estimates of prevalence in the normal population (Perna et al. 1997; Nascimento et al. 2002; Potoczek 2005). Both severe asthma in the past 4 weeks and severe lifetime asthma were associated with a significantly increased likelihood of PD (Goodwin et al. 2003). It has been reported that up to 40% of PD patients have a childhood history of respiratory diseases, particularly asthma and bronchitis (Verburg et al. 1995b). Furthermore, an increased incidence of PD in patients suffering from chronic obstructive pulmonary disease (COPD) has been reported (Karajgi et al. 1990). Interestingly, respiratory disorders and PD have been found to run in the same families. A common genetic susceptibility for PD and respiratory disorders has been suggested (Coryell et al. 2001; van Beek et al. 2005).

Unlike other anxiety disorders, the link between respiration and PD is explicitly mentioned in the most fundamental theories on the mechanisms of PD. Ley (1985) stated that unexpected somatic events (dyspnea and palpitations, in particular) are the consequence of a rise in blood alkalosis produced by hyperventilation. According to this theory, the occurrence of hyperventilation is a necessary factor for the occurrence of panic. In the past, a so-called hyperventilation provocation test was used to diagnose chronic hyperventilation. This method lacked both sensitivity and specificity and the diagnosis of hyperventilation syndrome appeared untenable (Hornsveld and Garssen 1996; Hornsveld et al. 1996). A second, quite influential, theory that attempts to explain panic suggests that panic attacks result from the catastrophic misinterpretation of certain internal bodily sensations (Clark 1986). The misinterpreted sensations are mainly those involved in normal anxiety responses (e.g., breathlessness). Clark suggested that the catastrophic misinterpretation of sensations accompanying hyperventilation

plays an important role in panic attacks. A third more biological theory proposed that CO_2 hypersensitivity in PD patients results from the malfunctioning of a "suffocation monitor". Normal shifts in physiological states, more specifically increased pCO_2 or decreased pH, are misinterpreted initiating a false alarm, i.e., panic attack (Klein 1993). In case this last theory would proof to describe the actual underlying mechanism of panic, malfunctioning of a critical system directly related to respiration is confirmed. This would explain most of the respiratory variability in PD and, at the same time, it would imply the specificity for this particular disorder.

3 Respiratory Variables in PD

The abundant literature concerning the link between respiration and PD clearly shows that this topic has stimulated researchers and inspired theories. The hypothesis of impaired respiratory functioning has led to studies investigating a plethora of respiratory parameters, such as respiratory rate (RR), partial pressure of CO_2 (pCO_2), tidal volume (TV), minute volume (MV), and more sophisticated techniques including approximate entropy. We recently reviewed the literature on respiratory parameters in PD (Niccolai et al. 2009). The following is based on the outcomes of this review.

3.1 Respiratory Rate

The easiest indicator of respiratory functioning is probably RR. Studies that investigated RR during baseline and resting conditions have consistently shown similar values in PD patients and controls. The same outcome was reported by one ambulatory monitoring study (Hoehn-Saric et al. 2004) and investigations during sleep onset and sleep (Koenigsberg et al. 1994; Stein et al. 1995). Different RR in PD patients compared to control subjects was found in some studies (Maddock and Carter 1991; Munjack et al. 1993; Wilhelm et al. 2001b), but the methodological design of these studies may well have influenced the outcomes.

With regard to panicogenic challenges, a similar result was found. Most studies measuring RR during the challenge phase did not find a different pattern in PD patients compared to controls. These studies involved either lactate infusion or 5% CO_2 inhalation (Schwartz et al. 1996; Rapee et al. 1992a; Bystritsky et al. 2000) as a respiratory challenge. One study reported increased RR in PD subjects 3–6 min after the start of lactate infusion during sleep (Koenigsberg et al. 1994). However, the difference between groups did not reach significance and, according to the authors, the increase was not impressive or consistent. Papp et al. (1993b) found higher RR in PD subjects compared to controls using the 35% CO_2 inhalation for 30 s.

However, this procedure is hardly comparable with others involving CO_2 inhalation. To our knowledge, this has never been replicated.

It has been proposed that PD patients are insufficiently capable of maintaining homeostasis (Perna et al. 2004). In this regard, it is very interesting to consider recovery from challenges when homeostasis needs to be restored. A few studies investigated RR during recovery from respiratory challenges. Two studies found higher doxapram induced RR in PD subjects than in controls (Lee et al. 1993; Abelson et al. 1996). Rapee et al. (1992a) found similar RR between medicated PD patients and controls following 5.5% CO_2 inhalation.

3.2 Partial Pressure of CO_2

Numerous studies have focused on baseline pCO_2. Outcomes show two major directions: towards diminished or towards similar pCO_2 levels in PD subjects compared to controls. The evidence for lower pCO_2 in PD patients than in healthy controls is most convincing as evidence comes from studies involving large sample size and focusing on resting conditions (Gorman et al. 1986; Papp et al. 1997; Liebowitz et al. 1985; Wilhelm et al. 2001b; Munjack et al. 1993; Ponto et al. 2002; Gorman et al. 1988; Rapee et al. 1992a; Holt and Andrews 1989). They provide true basal measurements, unbiased by the expectations of a challenge. Among those who did not report a difference in pCO_2 values between groups are studies with notable limitations concerning small sample size (Maddock and Carter 1991; Ponto et al. 2002; Kellner et al. 1998; Koenigsberg et al. 1994; Wilhelm et al. 2001a) or subjects' medication status (Pain et al. 1988; Holt and Andrews 1989; Rapee et al. 1992a). Antipanic medication can modulate respiratory physiology (Papp et al. 1993a; Gorman et al. 1997). Specifically, successful treatment of PD has been shown to normalize pCO_2 by increasing its values (Gorman et al. 1985).

Studies investigating the challenge phase have used either lactate infusion or inhalation of different concentrations of CO_2. During lactate infusion, PD subjects consistently showed decreased pCO_2 levels (Gorman et al. 1986; Liebowitz et al. 1985; Kellner et al. 1998) or a trend towards lower values (Koenigsberg et al. 1994). Moreover, in these studies nonpanicking patients and controls were compared and lower pCO_2 was reported for the first group.

Studies applying CO_2 inhalation found comparable results. Lower (Papp et al. 1997) or a trend towards lower (Ponto et al. 2002) pCO_2 levels in PD subjects compared to controls have been reported during the continuous inhalation of CO_2 concentrations around 6%. A few studies did not find a group difference, but they showed limitations concerning medication status, sex distribution (Rapee et al. 1992a), and type of challenge (Gorman et al. 1990). A different case is the 35% CO_2 inhalation challenge, in which a single vital capacity breath is taken and hypercapnia is immediate and lasts for about 7–16 s after exhalation (van den Hout and Griez 1985). Studies investigating pCO_2 level during the 35% CO_2 inhalation are limited, which is not surprising since the challenge procedure formally

exists of one inhalation and a breath holding period. Ponto et al. (2002) applied this challenge, followed by 10 s of rebreathing, and found lower pCO_2 levels in PD subjects than in controls.

Few studies have investigated the pCO_2 response during recovery from a challenge. Findings consistently report lower pCO_2 in PD patients compared to controls after both doxapram injection and CO_2 challenge. Lee et al. (1993) found lower pCO_2 in PD subjects compared to controls for the last 7 min of a 9-min recovery period from doxapram injection. Abelson et al. (1996) investigated 20 min of recovery from doxapram and reported reduced pCO_2 in PD subjects compared to controls persisting throughout the recovery phase and reaching significance during the last 5 min. After CO_2 inhalation, results consistently showed that lower pCO_2 in PD patients compared to controls was maintained for several minutes (Gorman et al. 1988, 1990; Papp et al. 1997). To our knowledge, only one study has reported similar pCO_2 values in PD subjects and controls during 7 min of recovery from 5.5% CO_2 inhalation (Rapee et al. 1992a). However, one major limitation of this study was that medication was not stopped before the test day, which makes the results less reliable. Moreover, as shown by other studies focusing on recovery phase, it appears that group differences in pCO_2 levels emerge after a period of time. It is possible that measuring challenge effects during recovery for only 7 min prevent finding a group difference in pCO_2.

3.3 Tidal Volume and Minute Volume

Findings from studies investigating TV and MV during baseline, sleep, or resting condition have mainly shown increased values in PD subjects compared to controls (Pain et al. 1988; Gorman et al. 1990; Stein et al. 1995; Abelson et al. 1996; Wilhelm et al. 2001b) or a tendency toward higher values in the PD group (Martinez et al. 1996; Papp et al. 1997). No evidence of lower TV and MV in PD patients compared to controls has been found. Some studies have reported no differences in TV and/or MV in PD subjects relative to healthy subjects (Gorman et al. 1988; Papp et al. 1993b; Yeragani et al. 2002).

The very few studies focusing on TV or MV during a respiratory challenge and/or the recovery period have shown inconsistent results. Normal TV in PD patients during respiratory challenges has been described (Abelson et al. 1996). Different TV reactivity between groups during recovery from 5% CO_2 inhalation has been reported as well (Papp et al. 1997). When subjects switched to room air, TV restored more slowly in patients than in controls. This was interpreted as a physiological response to CO_2 intolerance. Higher MV in PD subjects than in healthy subjects was found during a 30-s lasting 35% CO_2 inhalation (Papp et al. 1993b) and during recovery from doxapram injection (Lee et al. 1993; Abelson et al. 1996).

Overall, it appears that PD patients show a different reaction than controls to respiratory challenges with regard to their TV and MV.

3.4 Respiratory Variability, Sighing, and Approximate Entropy

Several studies found increased respiratory variability in PD subjects compared to controls during both baseline and resting conditions. Respiratory variability provides insight into fluctuations in respiration, which may play a role in susceptibility to panic (Wilhelm et al. 2001a). Abnormal respiratory regulation appears to render PD subjects more susceptible to heightened concentration of CO_2 in inhaled air (Martinez et al. 2001). In fact, PD subjects who panicked after CO_2 inhalation demonstrated the largest baseline respiratory variability in TV and MV. Other studies have confirmed increased baseline TV or MV variability in PD patients compared to controls (Gorman et al. 1988, 2001). Interestingly, Abelson et al. (2001) found that the increased TV irregularity in PD subjects was observed throughout the three phases of the experiment (adaptation, placebo, and postdoxapram phase). This stable respiratory feature may be suggestive of dysregulated neural circuits in the brainstem or midbrain levels in PD patients. Consistent with this, studies investigating sleep reported higher TV or MV variability in PD subjects compared to controls (Stein et al. 1995; Martinez et al. 1996). Presuming that sleep is a state during which anxiety is limited, these results could suggest that increased erratic breathing found in PD patients during baseline represents a physiological endophenotype. Increased respiratory variability in PD patients has also been found during recovery from the 35% CO_2 challenge. In a recent study from our laboratory, nonmedicated patients showed increased variability in both RR and pCO_2 compared to controls and medicated PD subjects (Niccolai et al. 2008).

More frequent and prominent sighs have been suggested to account for larger TV variability in PD patients compared to controls (Stein et al. 1995; Abelson et al. 2001). A higher frequency of sighs in PD subjects has been reported during resting state (Wilhelm et al. 2001a; Yeragani et al. 2002; Caldirola et al. 2004), baseline, and during/after a challenge (Schwartz et al. 1996; Abelson et al. 2001). It has also been found that patients had greater sighs than controls (Wilhelm et al. 2001a). Only one study did not find differences in the number of sighs between groups during sleep (Stein et al. 1995). However, the authors acknowledged that the enormous variability in sigh frequency shown by normal adults during sleep and the small sample size might explain the negative finding. Breath-by-breath variation in TV manifested by sighing is suggestive of a robust and fairly stable marker in PD patients (Abelson et al. 2001). Although the presence of sighs may not fully explain the irregularity in breathing patterns (Caldirola et al. 2004), it could contribute to the identification of respiratory etiopathological pathways in PD.

Apneic episodes also importantly contribute to respiratory variability. These episodes can be described as the absence of respiratory movement for a period of time that may range from l to 10 s. The higher number and the longer duration of apnea episodes appeared to distinguish PD patients from normal controls during baseline (Bystritsky and Shapiro 1992). Also, more frequent apnea episodes during

baseline seemed to predict panic attacks during CO_2 inhalation, both in patients and controls. Increased length and number of breathing pauses and increased variability in length of breathing cycle were found during baseline in panicking patients compared to the nonpanickers and normal controls by the same authors in a successive study (Bystritsky et al. 2000). The breathing pauses were found to persist or worsen during CO_2 inhalation. More frequent pauses in PD subjects' breathing relative to controls have also been found during sleep (Stein et al. 1995).

Results from studies applying approximate entropy, a measure of regularity of time series, are in line with the traditional measures of respiratory parameters (standard deviation and coefficient of variation). These findings suggest that PD subjects not only have a greater overall variability, but also a more chaotic pattern of breathing. Specifically, greater entropy in the respiratory function is suggestive of an intrinsic instability in the respiratory homeostasis, which would explain why hypercapnic challenges act as "disrupting factors" in PD patients, leading to panic attacks (Caldirola et al. 2004).

4 Respiration and Phobias

Phobias are particularly suitable to be subjected to psychological paradigms. These instances of acute fear are characterized by symptoms that transpire in specific situations. The physiological symptoms of an acute phobic reaction largely resemble the symptoms of a panic attack. In fact, phobic responses are often referred to as panic attacks, even though diagnostically, panic attacks are unexpected, spontaneous attacks, not triggered by a specific stimulus.

In essence, symptoms can be triggered by exposing patients to a phobic stimulus. The drawback of this kind of manipulation is that there is a myriad of possible approaches, resulting in a lack of standardization.

Basically, there are two different approaches – in vivo, and imaginal exposure – each with its own positive and negative aspects. The obvious advantages of imaginal exposure are the relative ease with which it can be conducted and its low costs. There are no special requirements other than a quiet room. However, it is hard to control the actual state of mind of the patient. Concerning in vivo exposure, basically, there are two options. Exposing the subject to the actual feared object or situation, such as a spider in spider phobia, or showing the subject images or movies of the relevant subject. Although the first might evoke the stronger reaction, the procedure has some drawbacks. It is often time consuming, guarantees little control over the environment, and can be costly. A great advantage of movies or pictures, is that it allows to study the responses to visual stimuli in, for example, fMRI paradigms. An alternative that is currently gaining more attention and which can be considered as a third option, is confrontation in a virtual environment.

In the following sections, some striking findings on respiratory symptoms in the different phobias are presented.

4.1 Social Phobia

Some interesting links exist between social phobia and PD (Horwath et al. 1995; Caldirola et al. 1997). From a diagnostic point of view, it can be difficult to distinguish a true unexpected panic attack from a situationally triggered attack in a socially phobic person. Symptomatically, there are many resemblances. The main discriminator are the cognitions of the patient during the attack. Whereas the social phobic will be afraid of the scrutiny and judgment of others, the PD patient will be mainly afraid of dying (suffocation), losing control, or going crazy. Remarkably, there have been some reports that showed increased sensitivity in social phobics for carbon dioxide (Gorman et al. 1990; Papp et al. 1993b; Caldirola et al. 1997). Unfortunately, the specific effect on respiratory symptoms was not addressed. In contrast, Pine et al (2000) subjected children who were diagnosed with social phobia to a 15-min period of 5% carbon dioxide inhalation and found no symptomatically defined hypersensitivity for carbon dioxide. However, this group consisted of only 10 children.

Public speaking tasks have been validated, in particular the Trier Social Stress Test (Kirschbaum et al. 1993), and activation of the sympathetic nervous system in social phobics during social confrontation has been demonstrated (Gerlach et al. 2003). However, despite the possible link between PD and social phobia and the distinct sympathetic activation during exposure, possible respiratory correlates of this disorder have not been addressed.

4.2 Blood Injury Phobia

Generally, acute anxiety states or, in other words, fear states, are known to be accompanied by sympathetic activation. Blood injury phobia (BIF) presents a bit of a difference in this regard. The vasovagal syncope, or presyncope, that often results from confrontation with the feared stimulus in BIF underlines not only a strong sympathetic response, but it could be related to an abnormal hemodynamic response, possibly not specifically related to the phobia itself (Accurso et al. 2001).

Respiratory symptoms have been addressed in some studies involving persons suffering from BIF. Respiration rate was measured under different circumstances among which were fear related and control movies. Sarlo et al. (2002) did not find a difference in RR between those different conditions. This finding was confirmed by Ritz et al. (2009) who also included a healthy control group. Interestingly, the latter authors included other respiratory parameters in addition to RR in which they did find differences. Specifically, during surgery films, MV and TV were significantly increased in BIF patients. In addition, irregularity of TV showed strong increases and there was a trend towards an increased sigh frequency in the movie condition. Concordantly, reduced pCO_2 levels have been reported by the same group (Ritz et al. 2005, 2009). In conclusion, there seems to be some indication that respiration is affected in BIF, especially during the acute state.

4.3 Other Phobias

The number of possible phobias is more or less endless. Even though the acute phobic response can be accompanied by a strong increase in respiration rate, detailed information on respiratory variables is limited. In a very early study of Prigatano and Johnson (1974), respiration rate and respiration amplitude in 11 spider phobic females was described in response to confrontation with pictures of spiders. No increase in RR was found in spider phobics during picture viewing both compared to a control group and to control slides. There was a trend towards significance with regard to respiration amplitude. Spider phobics showed larger respiratory amplitude in response to spider slides as compared to seaside or surgery slides. Yet, there was no difference in amplitude when phobic subject and controls were compared during the spider condition.

Two other phobias that have been described in literature with regard to respiration are driving and flying phobias. In both studies, respiratory variables were measured during real-life exposure. Wilhelm and Roth (1998) determined several respiratory variables in 14 flight phobics during a 12-min flight. Inspiratory pause showed the best discriminant validity for distinguishing phobics from controls, with phobics demonstrating extended pauses after inspiration of more than 20 s. A group effect was found for duty cycle, an index of inspiratory timing defined as inspiratory time/total breath time. This indicates a more tonic difference between the groups, possibly affected by anticipatory anxiety and differences in recovery. The remaining respiratory variables that were measured, knowing RR, MV, inspiratory flow rate, TV irregularity, did not discriminate between phobics and controls. A second study assessed multiple respiratory variables in 21 females suffering from driving phobia (Alpers et al. 2005). Differences between the control and the phobic group with regard to exposure were found for four different respiratory variables. Phobics showed lower ET pCO_2 during driving, and the effect size for distinguishing groups based on pCO_2 was large. Sigh rate showed a group effect with higher rates in phobics and duty cycle increased from quiet sitting to exposure, which was not the case in the control group. Additionally, respiratory variables related to pCO2 and sighing were determined. Larger variability in TV was present in phobics. Differences in mean RR and TV were not statistically significant.

5 Obsessive-Compulsive Disorder

Studies describing respiratory variables in obsessive-compulsive disorder (OCD) are rather scarce. Nevertheless, all of the relevant challenge paradigms have been described with the inclusion of respiratory parameters. Patients were studied under three conditions: relaxation, imaginal flooding, and in vivo exposure (Zohar et al. 1989) and during general stress tasks (Hoehn-Saric et al. 1995).

An early study by Zohar et al. (1989) included both RR and pCO_2. In vivo exposure resulted in anxiety ratings and obsessive-compulsive ratings that were

statistically higher than during imaginal exposure, which might lead to the conclusion that imaginal exposure is not as effective in evoking symptoms as real-life exposure. Blood pressure and heart rate were found to be significantly increased in the exposure trials as compared to the relaxation phase, but for both respiratory parameters no such effect was found. Unfortunately, this study included only 10 OCD patients and the variance in respiratory symptoms was rather large. Nevertheless, in contrast to the other physiological symptoms, pCO_2 values were lower during imaginal exposure than during relaxation. Strangely enough, during in vivo exposure, values equaled pCO_2 values obtained from the relaxation phase. Hoehn-Saric et al. (1995) subjected 23 OCD patients to two nonspecific stress tasks: the Divided Attention Task and the Risk Taking task. Physiological measurements included respiratory frequency but no group × task interaction effect was described for this variable. In this study, a decrease rather than an exaggeration of the physiologic response during psychological stress was described.

6 Generalized Anxiety Disorder

Somewhat more work has been performed on respiratory parameters in GAD. It might not be a coincidence that respiratory variables have received most attention in PD and GAD. In the DSM-II-R, "shortness of breath or smothering sensations" is described as a GAD symptom, whereas in other anxiety disorders other than GAD and PD, distinct descriptions of respiratory symptoms are not explicitly mentioned.

In an early study, Hoehn-Saric et al. (1989) performed a comparable study as described at the OCD section. Twenty female patients suffering from GAD were compared to a matched control group during baseline and during stress tasks. No differences in autonomic activity were reported during baseline. The stress tasks resulted in an increased respiratory frequency in both groups. Although GAD subjects reported increased difficulty in breathing during the tasks, respiratory frequency did not show a significant difference between groups in any of the conditions.

A more extended study (Wilhelm et al. 2001b) measured several respiratory variables during rest, including RR, TV, MV, duty cycle, inspiratory flow rate, ET CO_2, sighs, and apneas. In addition, breath-to-breath variability by Complex Demodulation was assessed as a measure of instability. Fifteen GAD patients were directly compared to PD patients ($n = 15$) and healthy control subjects ($n = 19$). Most respiratory variables were increased in PD patients as compared to the control group. GAD patients showed intermediate values, not significantly different from control values on any of the parameters. Duty cycle was significantly increased in GAD patients as compared to PD subjects. Group × time interactions were found for MV and inspiratory flow rate. Remarkably, GAD subjects showed a different response over time. GAD subjects showed a decline, whereas the other two groups slightly increased. The inclusion of variability indices proved valuable. None of the electrodermal or cardiovascular measures showed group effects,

whereas all of the respiratory variables did. This might indicate that respiratory variables are more sensitive indicators of anxiety or that they show better discriminative ability. Both patient groups showed increased variability as compared to controls on RR, TV, MV, and duty cycle. Variability in TV and MV was even larger in PD patients as compared to GAD patients, although the difference in TV disappeared when data was corrected for sighs. Six out of sixteen PD patients panicked during testing, and one GAD patient reported a symptomatic attack. Analyses were reproduced with exclusion of these subjects. As a result, some variables, among which duty cycle, lost significance. Removing these subjects resulted in an increased discriminative ability for pCO_2, for which this parameter became significantly smaller in PD patients as compared to GAD patients as well. In itself, this might seem counterintuitive. One would expect that during a panic attack, hyperventilation is most pronounced, resulting in decreased pCO_2 values. Yet, removing this specific group leaving only 10 PD, results in a significant difference between PD and GAD subjects. This seems to imply that the panicking subjects were responsible for increased variability.

Another direct comparison between PD and GAD patients was performed by Hoehn-Saric et al. (2004). Forty GAD subjects were compared to twenty-six PD patients and twenty-four control subjects during everyday activities. The only direct indication of respiratory functioning was RR. Subjectively, patients reported more difficulty breathing during the 6-h recording than control subjects. In PD subjects, this showed a sixfold increase during times when panic was reported. RR did not differentiate between groups. In addition, no statistically significant effects were found in the analysis of the relationship between RR and difficulty of breathing.

7 Posttraumatic Stress Disorder

Only limited information exists on respiratory variables in Posttraumatic Stress Disorder (PTSD). In PTSD, vivid memories or flashbacks can be accompanied by different autonomic symptoms including respiratory symptoms. In addition, increased heart rate and RR following a traumatic event have claimed to be predictors of subsequent PTSD (Bryant et al. 2008). One recent study (Blechert et al. 2007) describes different variables during a 5-min baseline period and during threat of shock in 23 PTSD patients, 26 PD patients, and 32 healthy control subjects. The following respiratory parameters were assessed: RR, TV, MV, duty cycle, sigh frequency, inspiratory flow rate, ET CO_2, and ribcage contribution to TV. Variability of respiratory cycle duration and TV was assessed using complex demodulation (frequency band: 0.004–0.14 Hz). Differences in respiratory variables were only found during baseline. Both patient groups had lower pCO_2 values as compared to control subjects, but this difference reached statistical significance only in the PD group. pCO_2 values in PTSD and PD patients were not statistically different. Additional differences in respiration were reported for sighing and ribcage contribution to TV. PTSD patients, but not PD patients, sighed more than control subjects

during baseline. Furthermore, PTSD patients showed less thoracic and more abdominal breathing than the other groups, indicated by lower ribcage contribution. None of the respiratory variables could discriminate between the diagnostic groups.

Unfortunately, to our knowledge there are no reports on respiratory variables in PTSD in which subjects were subjected to a disorder specific provocation paradigm, such as personalized trauma-related imagery, script-driven imagery method, or just simple exposure to trauma-related cues.

8 Discussion

The obvious abundance of literature on respiratory variables in PD is not remarkable considering the evident links between this physiological system and this specific psychiatric disorder. The frequent occurrence of respiratory symptoms seems relatively specific for PD, although respiratory symptoms have been described in other anxiety disorders as well. This is not surprising in itself, since increased RR is a normal physiological response to fear and anxiety – affective states that are characteristic for any anxiety disorder.

An important role of hyperventilation in PD has been suggested in different theories. Even though it has been shown that hyperventilation is not causally related to the occurrence of panic attacks, hyperventilation might be a phenomenon related to PD. As extensively reviewed by Niccolai et al. (2009), PD patients demonstrate decreased pCO_2 values under normal physiological circumstances and during respiratory challenges. With regard to basal values, different explanations have been suggested. Chronic hyperventilation would obviously explain low pCO_2 levels in PD subjects (Gorman et al. 1986). It has been proposed that chronic hyperventilation serves to maintain low levels of pCO_2 in order to avoid triggering of the CO_2 sensors. According to Klein's suffocation false alarm theory, triggering of these sensors would set off false alarms in these hypersensitive subjects. On the other hand, the great majority of studies do not show increased RR in PD subjects, which would be indicative of hyperventilation. However, chronic hyperventilation can also depend on TV. Increased TV has repeatedly reported in PD patients (Pain et al. 1988; Gorman et al. 1990; Stein et al. 1995; Abelson et al. 1996; Martinez et al. 1996; Papp et al. 1997; Wilhelm et al. 2001b). In other words, this indicates PD patients do not breathe faster, but breathe deeper than unaffected persons. Moreover, using disorder-specific challenges, MV and TV were increased in panicking patients as compared to nonpanicking PD subjects (Gorman et al. 1988). However, this is true for some specific phobias as well (Prigatano and Johnson 1974; Ritz et al. 2009), questioning the specificity of this measure. In contrast to resting conditions, increased RR has been found during panicogenic challenges in PD (Gorman et al. 1988, 2001). To our knowledge, this has not been reported for other anxiety disorders, with the limitation that data on respiratory parameters during disorder-specific challenges is scarce. Before drawing definite conclusions from this, one has to keep in mind that the validity of these indices as diagnostic

tools of chronic hyperventilation is questionable. The ultimate measures of hyperventilation are pCO_2, pH, and bicarbonates (Munjack et al. 1993). These very parameters have been investigated in PD patients by Gorman et al. (1986) using venous blood samples in rest. Mixed chronic and acute respiratory alkalosis was found, both characterized by low pCO_2 values and normal and elevated pH, respectively. In a subsequent study by the same group (Papp et al. 1989), arterial instead of venous pCO_2 was measured. Results were consistent with acute, but not chronic hyperventilation. In concordance, absence of chronic hyperventilation in PD patients was also reported in a more recent study investigating arterial blood gases (Zandbergen et al. 1993).

Clear insight into the issue of chronic hyperventilation may be provided by ambulatory monitoring studies. While experimental respiratory challenges directly influence respiration by provoking alkalosis or acidosis, ambulatory studies measure transcutaneous pCO_2 in a naturalistic setting. Therefore, data from ambulatory studies have greater external validity than those obtained in the laboratory, which, as a stressor-condition, may also influence psychophysiological recordings intrinsically. One study focusing on PD subjects reported no difference in transcutaneous pCO_2 between panic attacks and nonpanic control periods (Garssen et al. 1996). Despite the great value of ambulatory studies, to our knowledge no studies on pCO_2 in PD that included a control group, are available to date, possibly with the exception of one sleep study. During sleep onset, which is likely to be a good reflection of physiological activity at rest, no difference in pCO_2 was found between PD patients and control subjects (Koenigsberg et al. 1994). Even though more research needs to be performed, from the available data we can conclude that there are no clear indications of chronic hyperventilation in PD.

In addition to PD, reduced pCO_2 has been reported in BIF (Ritz et al. 2005) and driving phobia (Alpers et al. 2005) during disorder specific stress. Driving phobia has been associated to PD (Curtis et al. 1989), which could explain overlapping symptom profiles. However, this has been disputed by others (Antony et al. 1997). Lower baseline pCO_2 was found in both PD and in a mixed non-PD anxiety group consisting of mainly OCD patients and social phobics (van den Hout et al. 1992). In addition, Blechert et al. (2007) found decreased baseline pCO_2 values in PTSD patients that were not statistically from values of a group of PD patients. This indicates that decreased pCO_2, indicative of hyperventilation, is not specific for PD. Holt and Andrews (1989) suggested that hyperventilation may be intimately tied to anxious affect. The more anxious patients are, the more likely they are to show reduced pCO_2 levels. Furthermore, an explanation for decreased pCO_2 levels in anxiety disorders in general could be provided by increased levels of anticipatory anxiety. This is especially relevant when baseline values preceding an experimental stress paradigm are considered. Bystritsky et al. (2000) suggested that larger fluctuations in baseline breathing patterns in PD patients compared to controls are likely to reflect anticipatory anxiety. This could also apply to other anxiety disorders. The above seems to suggest that decreased pCO_2 does not constitute a specific trait marker of PD, but might be an indication of the current anxiety level.

In addition to decreased pCO_2 levels, both an increased frequency of sighs and greater sighs has been reported in PD (Schwartz et al. 1996; Abelson et al. 2001; Wilhelm et al. 2001a; Yeragani et al. 2002; Caldirola et al. 2004). It has been suggested that sighing adaptively keeps pCO_2 values below a depressed suffocation alarm threshold (Klein 1993). However, it should be noted that, in one of the studies reporting a higher rate of sighs in PD patients, the sighing pattern did not appear to be stimulated by increased pCO_2 or reduced TV (Wilhelm et al. 2001a). Another possible explanation for the adaptive effect of sighs is that they are efforts to overcome breathlessness (Klein 1993). Abelson et al. (2001) suggested that frequent sighing is a compensatory response in an attempt to reduce the sensation of dyspnea. According to others, it is more specific since sighing would distinguish between patients with chronic anxiety having frequent episodes of dyspnea from patients with various lung diseases (Tobin et al. 1983). However, with regard to the specificity of sighing for PD as compared to other anxiety disorders, some reservations have to be mentioned. A higher frequency of sighs in PD subjects has been reported (Schwartz et al. 1996; Abelson et al. 2001; Wilhelm et al. 2001a; Yeragani et al. 2002; Caldirola et al. 2004). However, increased levels of sighing as compared to control subjects has been reported in BIF (Ritz et al. 2009), driving phobia (Alpers et al. 2005), and PTSD (Blechert et al. 2007) as well, which seemed to be trait dependent and most pronounced for the latter two. In fact, the study in PTSD even showed increased sighing in PTSD as compared to PD subjects during a baseline period. Even though there is only limited data available on sighing in anxiety disorders, this does raise doubt on the specificity of this symptom for PD.

The increased comorbidity with respiratory disorders such as asthma and COPD that is often reported in PD, has also been described in other anxiety disorder but far less pronounced (Brenes 2003; Goodwin et al. 2003; Patten and Williams 2007). The fact that PD and respiratory disorders run in families, points to a shared genetic susceptibility, a trait that has not been reported for other anxiety disorders. This could indicate a specific vulnerability in PD patients related to the respiratory system. As a result, exaggerated fluctuations in biological substrates important for the regulation of respiration may emerge, that do not reach the threshold of conscious awareness. In line with this, increased variability and more chaotic breathing patterns have been described in PD (Wilhelm et al. 2001b; Yeragani et al. 2002; Caldirola et al. 2004). Although increased variability seems to be a promising candidate for a specific marker of panic, it has been reported in other anxiety disorders as well. In GAD, increased variability compared to values in control subjects was reported for RR, TV, MV, and duty cycle during quiet sitting (Wilhelm et al. 2001b). This study included both GAD and PD subjects. Only TV irregularity showed significantly increased values in PD subjects caused by sighing. Another study comparing healthy controls, PTSD and PD subjects during rest and during anticipation of electrical shock describes measures of variability in TV and respiratory cycle duration. No differences between either patient group or controls was described and it was reported that none of the respiratory variables discriminated between diagnostic groups. The only study describing respiratory variability during the active state was performed in driving phobics. A larger

variability in TV was reported in phobics as compared to control subjects during in vivo exposure.

Respiratory output is a physiological signal with complex dynamics that are not easily captured by linear statistics such as mean and standard deviation. A number of studies have, therefore, focused on nonlinear measures of respiration, which are likely to unravel the breath-by-breath complexity of respiratory dynamics. These more sophisticated measures include approximate entropy and other measures of chaos. Some studies have reported greater instability and higher levels of respiratory irregularity and complexity in PD subjects compared to healthy subjects in pCO_2, RR, TV, MV, and/or duty cycle (Wilhelm et al. 2001b; Yeragani et al. 2002; Caldirola et al. 2004).

The suggested inability of PD patients to preserve respiratory homeostasis explains the increased vulnerability of PD patients to specific panicogenic challenges. As stated before, these experimental procedures, in particular CO_2 inhalation, lactate infusion, and cholecystokinin infusion are known to exert a strong influence on respiration (Calverley et al. 1983; Liebowitz et al. 1984; Charney et al. 1985; Griez et al. 1987; Bradwejn et al. 1990). PD patients specifically show a more pronounced response to these challenges than both healthy control subjects and, in many instances, people suffering from other anxiety disorders (Den Boer et al. 1989; Cowley and Arana 1990; Bradwejn et al. 1991; van Megen et al. 1996; Perna et al. 1995; Verburg et al. 1995a). Comparable to other medical conditions, these provocation tests challenge the affected system and magnify subtle aberrations that otherwise may remain undetected. In addition, the fact that PD patients of the respiratory subtype show the most prominent response might point to a relationship between the degree of malfunctioning of the respiratory system and the response to provocation of this system. In fact, even in healthy volunteers the affective response to different dosages of carbon dioxide shows a dose response relationship, which is best predicted by respiratory symptoms (Colasanti et al. 2008).

In conclusion, even though disturbed respiration seems related to PD in many ways, simple, linear, measures of respiration do not discriminate between PD and other anxiety disorders. Since sympathetic activation, including respiratory adaptation, is such a general response to many situations, it should not come as a surprise that other conditions characterized by high anxiety levels show signs of affected respiration as well. Responses to general stress can differ substantially from responses to specific challenges. In PD, respiratory responses to panicogenic challenges have received major attention. Unfortunately, this is not the case for other anxiety disorders. Therefore, it seems too early to draw final conclusions on the specificity of respiratory symptoms with regard to the acute state. A related topic that deserves more attention is recovery. Assuming that PD is characterized by instability of the respiratory system, recovery after strong provocation of this system should be affected. Indeed, investigation of the recovery phase after either doxapram injection or CO_2 inhalation revealed lower pCO_2 and higher RR in PD patients compared to controls (Gorman et al. 1988, 1990; Lee et al. 1993; Abelson et al. 1996; Papp et al. 1997). To our knowledge, there are no reports on respiratory variables during recovery from acute state symptoms in other anxiety disorders.

Moreover, the underlying respiratory vulnerability in PD might not be a stable trait, which calls for more sensitive and sophisticated measures of respiratory variability, such as approximate entropy. Unfortunately, again this has been insufficiently investigated in other anxiety disorders to draw any conclusions.

At this point, there does not seem to be concrete evidence of a specific respiratory marker in PD. In fact, most parameters proved not to be specific. However, there are a few promising candidates left, coming from more sensitive and sophisticated methods that needs to be assessed in other anxiety disorders, preferably during or following disorder specific challenge paradigms.

Acknowledgments The authors wish to thank The Netherlands Organisation for Scientific Research. Dr. Van Duinen was granted with a Casimir Grant by this organization which enabled her to perform the current work.

References

Abelson JL, Nesse RM, Weg JG, Curtis GC (1996) Respiratory psychophysiology and anxiety: cognitive intervention in the doxapram model of panic. Psychosom Med 58:302–313

Abelson JL, Weg JG, Nesse RM, Curtis GC (2001) Persistent respiratory irregularity in patients with panic disorder. Biol Psychiatry 49:588–595

Accurso V, Winnicki M, Shamsuzzaman AS, Wenzel A, Johnson AK, Somers VK (2001) Predisposition to vasovagal syncope in subjects with blood/injury phobia. Circulation 104:903–907

Alpers GW, Wilhelm FH, Roth WT (2005) Psychophysiological assessment during exposure in driving phobic patients. J Abnorm Psychol 114:126–139

Antony MM, Brown TA, Barlow DH (1997) Heterogeneity among specific phobia types in DSM-IV. Behav Res Ther 35:1089–1100

APA (1994) Diagnostic and statistical manual of mental disorders. American Psychiatric Association, Washington, DC

Blechert J, Michael T, Grossman P, Lajtman M, Wilhelm FH (2007) Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. Psychosom Med 69:935–943

Bradwejn J, Koszycki D, Meterissian G (1990) Cholecystokinin-tetrapeptide induces panic attacks in patients with panic disorder. Can J Psychiatry 35:83–85

Bradwejn J, Koszycki D, Shriqui C (1991) Enhanced sensitivity to cholecystokinin tetrapeptide in panic disorder. Clinical and behavioral findings. Arch Gen Psychiatry 48:603–610

Brenes GA (2003) Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. Psychosom Med 65:963–970

Briggs AC, Stretch DD, Brandon S (1993) Subtyping of panic disorder by symptom profile. Br J Psychiatry 163:201–209

Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC (2008) A multisite study of initial respiration rate and heart rate as predictors of posttraumatic stress disorder. J Clin Psychiatry 69:1694–1701

Bystritsky A, Shapiro D (1992) Continuous physiological changes and subjective reports in panic patients: a preliminary methodological report. Biol Psychiatry 32:766–777

Bystritsky A, Craske M, Maidenberg E, Vapnik T, Shapiro D (2000) Autonomic reactivity of panic patients during a CO_2 inhalation procedure. Depress Anxiety 11:15–26

Caldirola D, Perna G, Arancio C, Bertani A, Bellodi L (1997) The 35% CO_2 challenge test in patients with social phobia. Psychiatry Res 71:41–48

Caldirola D, Bellodi L, Caumo A, Migliarese G, Perna G (2004) Approximate entropy of respiratory patterns in panic disorder. Am J Psychiatry 161:79–87
Calverley PM, Robson RH, Wraith PK, Prescott LF, Flenley DC (1983) The ventilatory effects of doxapram in normal man. Clin Sci (Lond) 65:65–69
Charney DS, Heninger GR, Jatlow PI (1985) Increased anxiogenic effects of caffeine in panic disorders. Arch Gen Psychiatry 42:233–243
Clark DM (1986) A cognitive approach to panic. Behav Res Ther 24:461–470
Colasanti A, Salamon E, Schruers K, van Diest R, van Duinen M, Griez EJ (2008) Carbon dioxide-induced emotion and respiratory symptoms in healthy volunteers. Neuropsychopharmacology 33(13):3103–3110
Coryell W, Fyer A, Pine D, Martinez J, Arndt S (2001) Aberrant respiratory sensitivity to CO(2) as a trait of familial panic disorder. Biol Psychiatry 49:582–587
Cowley DS, Arana GW (1990) The diagnostic utility of lactate sensitivity in panic disorder. Arch Gen Psychiatry 47:277–284
Curtis GC, Himle JA, Lewis JA, Lee Y (1989) Specific situational phobias: Variant of agoraphobia? In: Uo M (ed) Report to the DSM-IV anxiety disorders work-group. Ann Arbor, MI
Den Boer JA, Westenberg HG, Klompmakers AA, van Lint LE (1989) Behavioral biochemical and neuroendocrine concomitants of lactate-induced panic anxiety. Biol Psychiatry 26:612–622
Dudley DL, Martin CJ, Holmes TH (1968) Dyspnea: psychologic and physiologic observations. J Psychosom Res 11:325–339
Garssen B, Buikhuisen M, van Dyck R (1996) Hyperventilation and panic attacks. Am J Psychiatry 153:513–518
Gerlach AL, Wilhelm FH, Roth WT (2003) Embarrassment and social phobia: the role of parasympathetic activation. J Anxiety Disord 17:197–210
Goodwin RD, Jacobi F, Thefeld W (2003) Mental disorders and asthma in the community. Arch Gen Psychiatry 60:1125–1130
Gorman JM, Fyer AJ, Ross DC, Cohen BS, Martinez JM, Liebowitz MR, Klein DF (1985) Normalization of venous pH, pCO_2, and bicarbonate levels after blockade of panic attacks. Psychiatry Res 14:57–65
Gorman JM, Cohen BS, Liebowitz MR, Fyer AJ, Ross D, Davies SO, Klein DF (1986) Blood gas changes and hypophosphatemia in lactate-induced panic. Arch Gen Psychiatry 43:1067–1071
Gorman JM, Fyer MR, Goetz R, Askanazi J, Liebowitz MR, Fyer AJ, Kinney J, Klein DF (1988) Ventilatory physiology of patients with panic disorder. Arch Gen Psychiatry 45:31–39
Gorman JM, Papp LA, Martinez J, Goetz RR, Hollander E, Liebowitz MR, Jordan F (1990) High-dose carbon dioxide challenge test in anxiety disorder patients. Biol Psychiatry 28:743–757
Gorman JM, Browne ST, Papp LA, Martinez J, Welkowitz L, Coplan JD, Goetz RR, Kent J, Klein DF (1997) Effect of antipanic treatment on response to carbon dioxide. Biol Psychiatry 42:982–991
Gorman JM, Kent J, Martinez J, Browne S, Coplan J, Papp LA (2001) Physiological changes during carbon dioxide inhalation in patients with panic disorder, major depression, and premenstrual dysphoric disorder: evidence for a central fear mechanism. Arch Gen Psychiatry 58:125–131
Griez EJ, Lousberg H, van den Hout MA, van der Molen GM (1987) CO_2 vulnerability in panic disorder. Psychiatry Res 20:87–95
Han JN, Zhu YJ, Li SW, Luo DM, Hu Z, Van Diest I, De Peuter S, Van de Woestijne KP, Van den Bergh O (2004) Medically unexplained dyspnea: psychophysiological characteristics and role of breathing therapy. Chin Med J (Engl) 117:6–13
Hoehn-Saric R, McLeod DR, Zimmerli WD (1989) Somatic manifestations in women with generalized anxiety disorder. Psychophysiological responses to psychological stress. Arch Gen Psychiatry 46:1113–1119
Hoehn-Saric R, McLeod DR, Hipsley P (1995) Is hyperarousal essential to obsessive-compulsive disorder? Diminished physiologic flexibility, but not hyperarousal, characterizes patients with obsessive-compulsive disorder. Arch Gen Psychiatry 52:688–693

Hoehn-Saric R, McLeod DR, Funderburk F, Kowalski P (2004) Somatic symptoms and physiologic responses in generalized anxiety disorder and panic disorder: an ambulatory monitor study. Arch Gen Psychiatry 61:913–921

Holt PE, Andrews G (1989) Hyperventilation and anxiety in panic disorder, social phobia, GAD and normal controls. Behav Res Ther 27:453–460

Hornsveld H, Garssen B (1996) The low specificity of the hyperventilation provocation test. J Psychosom Res 41:435–449

Hornsveld H, Garssen B (1997) Hyperventilation syndrome: an elegant but scientifically untenable concept. Neth J Med 50:13–20

Hornsveld HK, Garssen B, Dop MJ, van Spiegel PI, de Haes JC (1996) Double-blind placebo-controlled study of the hyperventilation provocation test and the validity of the hyperventilation syndrome. Lancet 348:154–158

Horwath E, Wolk SI, Goldstein RB, Wickramaratne P, Sobin C, Adams P, Lish JD, Weissman MM (1995) Is the comorbidity between social phobia and panic disorder due to familial cotransmission or other factors? Arch Gen Psychiatry 52:574–582

Karajgi B, Rifkin A, Doddi S, Kolli R (1990) The prevalence of anxiety disorders in patients with chronic obstructive pulmonary disease. Am J Psychiatry 147:200–201

Kellner M, Knaudt K, Jahn H, Holsboer F, Wiedemann K (1998) Atrial natriuretic hormone in lactate-induced panic attacks: mode of release and endocrine and pathophysiological consequences. J Psychiatr Res 32:37–48

Kirschbaum C, Pirke KM, Hellhammer DH (1993) The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28:76–81

Klein DF (1993) False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. Arch Gen Psychiatry 50:306–317

Koenigsberg HW, Pollak CP, Fine J, Kakuma T (1994) Cardiac and respiratory activity in panic disorder: effects of sleep and sleep lactate infusions. Am J Psychiatry 151:1148–1152

Lee YJ, Curtis GC, Weg JG, Abelson JL, Modell JG, Campbell KM (1993) Panic attacks induced by doxapram. Biol Psychiatry 33:295–297

Ley R (1985) Agoraphobia, the panic attack and the hyperventilation syndrome. Behav Res Ther 23:79–81

Liebowitz MR, Fyer AJ, Gorman JM, Dillon D, Appleby IL, Levy G, Anderson S, Levitt M, Palij M, Davies SO et al (1984) Lactate provocation of panic attacks. I. Clinical and behavioral findings. Arch Gen Psychiatry 41:764–770

Liebowitz MR, Gorman JM, Fyer AJ, Levitt M, Dillon D, Levy G, Appleby IL, Anderson S, Palij M, Davies SO, Klein DF (1985) Lactate provocation of panic attacks. II. Biochemical and physiological findings. Arch Gen Psychiatry 42:709–719

Maddock RJ, Carter CS (1991) Hyperventilation-induced panic attacks in panic disorder with agoraphobia. Biol Psychiatry 29:843–854

Martinez JM, Papp LA, Coplan JD, Anderson DE, Mueller CM, Klein DF, Gorman JM (1996) Ambulatory monitoring of respiration in anxiety. Anxiety 2:296–302

Martinez JM, Kent JM, Coplan JD, Browne ST, Papp LA, Sullivan GM, Kleber M, Perepletchikova F, Fyer AJ, Klein DF, Gorman JM (2001) Respiratory variability in panic disorder. Depress Anxiety 14:232–237

Munjack DJ, Brown RA, McDowell DE (1993) Existence of hyperventilation in panic disorder with and without agoraphobia, GAD, and normals: Implications for the cognitive theory of panic. J Anxiety Disord 7:37–48

Nardi AE, Valenca AM, Mezzasalma MA, Lopes FL, Nascimento I, Veras AB, Freire RC, de-Melo-Neto VL, Zin WA (2006) 35% Carbon dioxide and breath-holding challenge tests in panic disorder: a comparison with spontaneous panic attacks. Depress Anxiety 23: 236–244

Nascimento I, Nardi AE, Valenca AM, Lopes FL, Mezzasalma MA, Nascentes R, Zin WA (2002) Psychiatric disorders in asthmatic outpatients. Psychiatry Res 110:73–80

Niccolai V, van Duinen MA, Griez EJ (2008) Objective and subjective measures in recovery from a 35% carbon dioxide challenge. Can J Psychiatry 53:737–744
Niccolai V, Van Duinen MA, Griez EJL (2009) Respiratory patterns in panic disorder reviewed: a focus on biological challenge tests. Acta Psychiatr Scand 120(3):167–177
Pain MC, Biddle N, Tiller JW (1988) Panic disorder, the ventilatory response to carbon dioxide and respiratory variables. Psychosom Med 50:541–548
Papp LA, Martinez JM, Klein DF, Ross D, Liebowitz MR, Fyer AJ, Hollander E, Gorman JM (1989) Arterial blood gas changes in panic disorder and lactate-induced panic. Psychiatry Res 28:171–180
Papp LA, Klein DF, Gorman JM (1993a) Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. Am J Psychiatry 150:1149–1157
Papp LA, Klein DF, Martinez J, Schneier F, Cole R, Liebowitz MR, Hollander E, Fyer AJ, Jordan F, Gorman JM (1993b) Diagnostic and substance specificity of carbon-dioxide-induced panic. Am J Psychiatry 150:250–257
Papp LA, Martinez JM, Klein DF, Coplan JD, Norman RG, Cole R, de Jesus MJ, Ross D, Goetz R, Gorman JM (1997) Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. Am J Psychiatry 154:1557–1565
Patten SB, Williams JV (2007) Chronic obstructive lung diseases and prevalence of mood, anxiety, and substance-use disorders in a large population sample. Psychosomatics 48:496–501
Perna G, Bertani A, Arancio C, Ronchi P, Bellodi L (1995) Laboratory response of patients with panic and obsessive-compulsive disorders to 35% CO_2 challenges. Am J Psychiatry 152:85–89
Perna G, Bertani A, Politi E, Colombo G, Bellodi L (1997) Asthma and panic attacks. Biol Psychiatry 42:625–630
Perna G, Caldirola D, Bellodi L (2004) Panic disorder: from respiration to the homeostatic brain. Acta Neuropsychiatr 16:57–67
Pine DS, Klein RG, Coplan JD, Papp LA, Hoven CW, Martinez J, Kovalenko P, Mandell DJ, Moreau D, Klein DF, Gorman JM (2000) Differential carbon dioxide sensitivity in childhood anxiety disorders and nonill comparison group. Arch Gen Psychiatry 57:960–967
Ponto LL, Kathol RG, Kettelkamp R, Watkins GL, Richmond JC, Clark J, Hichwa RD (2002) Global cerebral blood flow after CO_2 inhalation in normal subjects and patients with panic disorder determined with [15O]water and PET. J Anxiety Disord 16:247–258
Potoczek A (2005) Difficult asthma, stress and panic disorder. Psychiatr Pol 39:51–66
Prigatano GP, Johnson HJ (1974) Autonomic nervous system changes associated with a spider phobic reaction. J Abnorm Psychol 83:169–177
Rapee RM, Brown TA, Antony MM, Barlow DH (1992a) Response to hyperventilation and inhalation of 5.5% carbon dioxide-enriched air across the DSM-III-R anxiety disorders. J Abnorm Psychol 101:538–552
Rapee RM, Sanderson WC, McCauley PA, Di Nardo PA (1992b) Differences in reported symptom profile between panic disorder and other DSM-III-R anxiety disorders. Behav Res Ther 30:45–52
Ritz T, Wilhelm FH, Gerlach AL, Kullowatz A, Roth WT (2005) End-tidal pCO_2 in blood phobics during viewing of emotion- and disease-related films. Psychosom Med 67:661–668
Ritz T, Wilhelm FH, Meuret AE, Gerlach AL, Roth WT (2009) Do blood phobia patients hyperventilate during exposure by breathing faster, deeper, or both? Depress Anxiety 26: E60–67
Sarlo M, Palomba D, Angrilli A, Stegagno L (2002) Blood phobia and spider phobia: two specific phobias with different autonomic cardiac modulations. Biol Psychol 60:91–108
Schwartz GE, Goetz RR, Klein DF, Endicott J, Gorman JM (1996) Tidal volume of respiration and "sighing" as indicators of breathing irregularities in panic disorder patients. Anxiety 2:145–148
Stein MB, Millar TW, Larsen DK, Kryger MH (1995) Irregular breathing during sleep in patients with panic disorder. Am J Psychiatry 152:1168–1173

Tobin MJ, Chadha TS, Jenouri G, Birch SJ, Gazeroglu HB, Sackner MA (1983) Breathing patterns. 2. Diseased subjects. Chest 84:286–294

Valenca AM, Nardi AE, Nascimento I, Zin WA, Versiani M (2002) Respiratory panic disorder subtype and sensitivity to the carbon dioxide challenge test. Braz J Med Biol Res 35:783–788

van Beek N, Schruers KR, Griez EJ (2005) Prevalence of respiratory disorders in first-degree relatives of panic disorder patients. J Affect Disord 87:337–340

van den Hout MA, Griez E (1985) Peripheral panic symptoms occur during changes in alveolar carbon dioxide. Compr Psychiatry 26:381–387

van den Hout MA, Hoekstra R, Arntz A, Christiaanse M, Ranschaert W, Schouten E (1992) Hyperventilation is not diagnostically specific to panic patients. Psychosom Med 54:182–191

van Megen HJ, Westenberg HG, Den Boer JA, Kahn RS (1996) The panic-inducing properties of the cholecystokinin tetrapeptide CCK4 in patients with panic disorder. Eur Neuropsychopharmacol 6:187–194

Verburg K, Griez E, Meijer J, Pols H (1995a) Discrimination between panic disorder and generalized anxiety disorder by 35% carbon dioxide challenge. Am J Psychiatry 152:1081–1083

Verburg K, Griez E, Meijer J, Pols H (1995b) Respiratory disorders as a possible predisposing factor for panic disorder. J Affect Disord 33:129–134

Wilhelm FH, Roth WT (1998) Taking the laboratory to the skies: ambulatory assessment of self-report, autonomic, and respiratory responses in flying phobia. Psychophysiology 35:596–606

Wilhelm FH, Trabert W, Roth WT (2001a) Characteristics of sighing in panic disorder. Biol Psychiatry 49:606–614

Wilhelm FH, Trabert W, Roth WT (2001b) Physiologic instability in panic disorder and generalized anxiety disorder. Biol Psychiatry 49:596–605

Yeragani VK, Radhakrishna RK, Tancer M, Uhde T (2002) Nonlinear measures of respiration: respiratory irregularity and increased chaos of respiration in patients with panic disorder. Neuropsychobiology 46:111–120

Zandbergen J, Bright M, Pols H, Fernandez I, de Loof C, Griez EJ (1991) Higher lifetime prevalence of respiratory diseases in panic disorder? Am J Psychiatry 148:1583–1585

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

Zohar J, Insel TR, Berman KF, Foa EB, Hill JL, Weinberger DR (1989) Anxiety and cerebral blood flow during behavioral challenge. Dissociation of central from peripheral and subjective measures. Arch Gen Psychiatry 46:505–510