

# Clinical features of panic patients sensitive to hyperventilation or breath-holding methods for inducing panic attacks

A.E. Nardi<sup>1</sup>, A.M. Valença<sup>1</sup>,  
F.L. Lopes<sup>1</sup>, I. Nascimento<sup>1</sup>,  
M.A. Mezzasalma<sup>1</sup>  
and W.A. Zin<sup>2</sup>

<sup>1</sup>Laboratório de Pânico e Respiração, Instituto de Psiquiatria, and  
<sup>2</sup>Laboratório de Fisiologia Respiratória, Instituto de Biofísica Carlos Chagas Filho,  
Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil

## Abstract

Our aim was to compare the clinical features of panic disorder (PD) patients sensitive to hyperventilation or breath-holding methods of inducing panic attacks. Eighty-five PD patients were submitted to both a hyperventilation challenge test and a breath-holding test. They were asked to hyperventilate (30 breaths/min) for 4 min and a week later to hold their breath for as long as possible, four times with a 2-min interval. Anxiety scales were applied before and after the tests. We selected the patients who responded with a panic attack to just one of the tests, i.e., those who had a panic attack after hyperventilating (HPA, N = 24, 16 females, 8 males, mean age  $\pm$  SD = 38.5  $\pm$  12.7 years) and those who had a panic attack after breath holding (BHPA, N = 20, 11 females, 9 males, mean age  $\pm$  SD = 42.1  $\pm$  10.6 years). Both groups had similar ( $\chi^2 = 1.28$ , d.f. = 1, P = 0.672) respiratory symptoms (fear of dying, chest/pain discomfort, shortness of breath, paresthesias, and feelings of choking) during a panic attack. The criteria of Briggs et al. [*British Journal of Psychiatry*, 1993; 163: 201-209] for respiratory PD subtype were fulfilled by 18 (75.0%) HPA patients and by 14 (70.0%) BHPA patients. The HPA group had a later onset of the disease compared to BHPA patients (37.9  $\pm$  11.0 vs 21.3  $\pm$  12.9 years old, Mann-Whitney, P < 0.001), and had a higher family prevalence of PD (70.8 vs 25.0%,  $\chi^2 = 19.65$ , d.f. = 1, P = 0.041). Our data suggest that these two groups - HPA and BHPA patients - may be specific subtypes of PD.

## Key words

- Anxiety disorder
- Challenge tests
- Panic disorder
- Hyperventilation
- Breath holding

## Correspondence

A.E. Nardi  
Laboratório de Pânico e Respiração  
Instituto de Psiquiatria, UFRJ  
R. Visconde de Pirajá, 407/702  
22410-003 Rio de Janeiro, RJ  
Brasil  
Fax: +55-21-2523-6839  
E-mail: aenardi@novanet.com.br

Research supported by CNPq  
(No. 300500/93-9).

Received February 6, 2003  
Accepted October 23, 2003

## Introduction

Respiratory tests have been fruitful in generating hypotheses about panic disorder (PD) (1). The connection between respiratory system and PD has been reported in the medical literature (2). Klein (1) proposed

that spontaneous panic attacks occur when the brain's suffocation monitor erroneously signals a lack of useful air, maladaptively triggering an evolved suffocation alarm system. Such a dysfunction would make an individual vulnerable to "false suffocation alarms", namely panic attacks. Carbon diox-

ide (CO<sub>2</sub>) sensitivity may be an aspect of a hypersensitive suffocation detector (1).

Respiratory abnormalities are associated with anxiety, particularly with panic attacks (3,4). Misinterpretation of induced respiratory symptoms increases fear and autonomic activity resulting in increasing respiratory frequency that will further dissipate CO<sub>2</sub> and intensify hypocapnic symptoms (3). PD patients exhibit both behavioral and physiological abnormal responses to respiratory challenge tests (5,6). Symptoms such as shortness of breath, "empty-head" feeling, dizziness, paresthesias, and tachypnea have been described in the psychiatric and respiratory physiology literature related to PD (3,7). Panic patients report significantly more panic attacks and anxiety during the respiratory challenge tests than normal volunteers (3,4,8).

The inhalation of high concentrations of CO<sub>2</sub> has also consistently been shown to increase anxiety and induce panic attacks in PD patients (9,10). A CO<sub>2</sub>-induced panic attack closely resembles the panic attack PD patients experience outside the laboratory (9) and is one of the most reliable panicogenic agents (9,10). A simple and natural method of inducing endogenous CO<sub>2</sub> increase may be breath holding. The provocation of anxiety by an increase in CO<sub>2</sub>, as in breath holding, may be a reliable marker of panic.

Hyperventilating at 30 breaths per minute, although causing a significant drop in end-tidal CO<sub>2</sub> to conventionally accepted levels of hypocapnia, seems to be a less reliable panicogenic challenge than CO<sub>2</sub> inhalation (7). However, for a small group of PD patients hyperventilation may be a safe and easy test for a more precise diagnosis. Indeed, hyperventilation has been considered to be a cause, a correlate, or a consequence of panic attacks (11).

We have been studying the relationship between hyperventilation-(HPA) and breath-holding-induced panic attacks (BHPA) (12-16). Although in all investigations the PD

group had a higher sensitivity to the respiratory challenge tests, some patients responded selectively to either hyperventilation or breath holding. It is not clear, however, if these two groups present distinct clinical characteristics. Thus, the objective of the present study was to compare the clinical features of these two groups.

## Patients and Methods

We randomly selected 85 PD patients from the Laboratory of Panic and Respiration of the Federal University of Rio de Janeiro. The patients had not participated in any other respiratory challenge test. They included 58 women and 27 men with a mean age ( $\pm$  SD) of  $41.6 \pm 13.5$  years. All patients were submitted to the two tests, separated by a one-week interval.

After the subjects received a clinical diagnosis of PD during an ordinary clinical interview held by a psychiatrist, they were interviewed by a second clinician using the Structured Clinical Interview Diagnostic (SCID) (17) for DSM-IV (18). The subject was only enrolled in the study if a consensus diagnosis could be reached between the two psychiatrists. Patients who met DSM-IV (18) criteria for bipolar disorder, obsessive-compulsive disorder, schizophrenia, delusional or psychotic disorders, organic brain syndrome, severe personality disorder, epilepsy, or substance abuse or dependence (during the previous year) were excluded. Patients with comorbid dysthymia, generalized anxiety disorder, or past major depression were included if PD was judged to be the principal diagnosis.

The protocol was explained to the subjects, who signed a voluntary written consent to participate. Our Institute of Psychiatry, UFRJ Ethics Committee approved the protocol, which complied with the principles of the Declaration of Helsinki. The subjects were informed that they would be asked to hyperventilate room air and one week later

to hold their breath four times. They also were informed that the procedure was not dangerous but that anxiety symptoms could occur during the session.

The inclusion criteria were: 18 to 55 years of age, occurrence of at least three panic attacks in the two weeks before the challenge test day, no use of any psychotropic drugs for at least one week by any subject, and a negative urine test for benzodiazepines and other medications before the tests.

Exclusion criteria were: unstable medical condition, cognitive-behavior psychotherapy during the study, use of any regular antipsychotic, antidepressant, regular benzodiazepine or nonbenzodiazepine anxiolytic medication for 4 weeks, or fluoxetine for 5 weeks before the test; or the presence of suicidal risk. Subjects with a history of respiratory disease and smokers were also excluded.

All subjects underwent physical examination and laboratory exams to ensure they were healthy enough to participate in the respiratory challenge tests. They had no respiratory or cardiovascular abnormalities and were free of caffeine ingestion for 24 h before the tests.

The tests were conducted in the usual examination room, with no changes made in the environment. All subjects were asked to relax for 10 min. We then checked respiratory frequency, pulse, and blood pressure. These measurements were repeated 1 and 5 min after the test. To measure the baseline anxiety level subjects were asked to complete before the test the Subjective Units of Disturbance Scale (SUDS), a semiquantitative evaluation method ranging from 0 (no anxiety) to 10 (maximum anxiety) (19), and the Diagnostic Symptom Questionnaire (DSQ) (19) adapted for DSM-IV in which the presence and level of discomfort of panic symptoms experienced after the test were rated on a 0 to 4 point scale (0 = none, 4 = very severe). The scales had been evaluated

by back translation. On the basis of the DSQ, the presence of a panic attack was defined when the subject presented: 1) four or more symptoms of a panic attack from the DSM-IV, 2) at least one of the cognitive symptoms of a panic attack from the DSM-IV (e.g., fear of dying or of losing sanity or control), 3) feeling of panic or fear, similar to spontaneous panic attacks recorded on a card which the raters were not permitted to observe, and 4) agreement about clinical panic attack diagnosis between two test-blinded raters. The comparison of the two rater scores was done after the test. The feeling of a panic attack reported by the subjects was also examined in order to compare agreement between raters and subjects.

After the hyperventilating test had been explained the subjects were submitted to a 30-s training period. The subjects then relaxed for an additional 10-min period, after which hyperventilation (30 respiratory movements per minute over a period of 4 min) was induced, with a rater counting aloud the ventilatory movements. Immediately after this period we evaluated the level of anxiety and the presence of a panic attack.

The breath-holding test consisted of four trials as used by van der Does (20). The first three trials had a 1-min anticipation period, followed by cessation of breathing at functional residual capacity for maximum duration, and a 2-min recovery period. Subjects were instructed to stop breathing following a normal (i.e., not forced) exhalation and to maintain the cessation for as long as possible. The fourth trial consisted of breath holding after a full vital capacity breath. All patients used an easily self-removable nose-clip. Immediately after this period we evaluated the level of anxiety and the presence of a panic attack. A chronometer was used to measure the breath-holding time.

#### Statistical analysis

Panic rates of symptoms for the two

groups were compared by the  $\chi^2$  test. Data concerning the effects of hyperventilation and time of observation were tested by two-way ANOVA with repeated measures for time and independent groups for SUDS (before and after). Current age and age at the beginning of the disorder were compared by the Mann-Whitney test. Gender, educational level, marital status, occupation, and ethnicity were compared using  $\chi^2$  tests. Pair-wise comparisons of the groups were performed using

Fisher's protected least significant difference method. The level of significance was set at 5%.

## Results

In our initial sample (N = 85), 44 (51.8%) patients had a panic attack in one of the respiratory tests, 25 (29.4%) patients had a panic attack in both tests, and 16 (18.8%) had no panic attack in any test.

The demographic and clinical features of the HPA (N = 24) and BHPA (N = 20) groups can be seen in Table 1. The groups did not differ in gender, age, educational level, marital status, occupation, incidence of previous depressive episodes, or previous psychiatric treatment (Table 1). The HPA group had a higher frequency of a family history of PD and a later onset of the PD (Table 1).

Table 2 shows the SUDS level measurement before and after the tests. Both groups were highly sensitive and had a similar increase in anxiety level after the tests.

Patients with 4 or more respiratory symptoms (N = 27; 61.4%) had more spontaneous panic attacks (mean  $\pm$  SD: 9.5  $\pm$  9.6 in the past 4 weeks) than did patients with fewer respiratory symptoms (N = 17; 38.6%; mean  $\pm$  SD: 4.3  $\pm$  4.1). This difference was statistically significant (ANOVA, d.f. = 1,40; F = 12.76; P = 0.011). Patients with four or more respiratory symptoms had significantly more situational panic attacks (8.8; SD = 3.9) than did the remaining patients (3.2  $\pm$  4.7; ANOVA: d.f. = 1,40; F = 9.77; P = 0.008). The HPA group (N = 24) had 14 (58.3%) respiratory subtype PD patients and the BHPA group (N = 20) had 13 (65.0%) respiratory subtype PD patients ( $\chi^2 = 1.67$ , d.f. = 1, P = 0.562).

The frequency of panic attack symptoms in the HPA group vs the BHPA group can be seen in Table 3. There were no differences between groups. Symptoms appearing more frequently were fear of dying, chest pain/

Table 1. Demographic and clinical characteristics of the hyperventilation-sensitive panic attack group (HPA) vs the breath-holding-sensitive panic attack group (BHPA).

Sex	Male	Female
HPA (N = 24)	8 (33.3)	16 (66.7)
BHPA (N = 20)	9 (45.0)	11 (55.0)
Age (years $\pm$ SD)		
HPA	38.5 $\pm$ 12.7	
BHPA	42.1 $\pm$ 10.6	
Educational level <sup>1</sup>	High	Low
HPA (N = 24)	19 (62.5)	5 (37.5)
BHPA (N = 20)	16 (80.0)	4 (20.0)
Marital status	Married	Not married
HPA (N = 24)	15 (44.3)	9 (55.7)
BHPA (N = 20)	12 (60.0)	8 (40.0)
Occupation	Active	Inactive
HPA (N = 24)	16 (66.7)	8 (33.3)
BHPA (N = 20)	17 (85.0)	3 (15.0)
Family history of panic disorder*	Yes	No
HPA (N = 24)	17 (70.8)	7 (29.2)
BHPA (N = 20)	5 (25.0)	15 (75.0)
Age at onset of the disease (years $\pm$ SD)		
HPA	37.9 $\pm$ 11.0 <sup>+</sup>	
BHPA	21.3 $\pm$ 12.9	
Patients with previous depressive episodes <sup>2</sup>	Yes	No
HPA (N = 24)	20 (83.3)	4 (16.7)
BHPA (N = 20)	12 (60.0)	8 (40.0)

Data are reported as number (%) of patients except for age and age at onset of the disease which are reported as mean ( $\pm$  SD) number of years.

<sup>1</sup>High = 12 or more years of study; low = less than 12 years of study. <sup>2</sup>Obtained by a clinical interview with the patient. \* $\chi^2 = 19.65$ , d.f. = 1, P = 0.041. <sup>+</sup>P < 0.001 compared to BHPA (Mann-Whitney test).

discomfort, shortness of breath, paresthesias, and feelings of choking.

## Discussion

In the present study we compared the clinical features of PD patients who had a panic attack after a hyperventilation challenge test with those of patients who had an attack after a breath-holding test. The demographic and clinical characteristics of both groups were very similar but the HPA group had a higher frequency of a family history of PD, and a later onset of the disease (Table 1). The subjective level of anxiety after the respiratory tests (Table 2) was similar in the two groups. PD subtypes have been described in the literature (21,22). Briggs et al. (21) studied the description of the last and most severe panic attack of 1108 PD patients, which were divided into two groups according to the presence or absence of prominent respiratory symptoms. They found that the group with prominent respiratory symptoms had more spontaneous panic attacks and had better responses to imipramine, while patients from the non-respiratory subgroup had more situational panic attacks and had better responses to alprazolam.

Cognitive factors are also present in the respiratory tests (23). The CO<sub>2</sub> and lactate infusion tests can be easily compared with a placebo test but the difficulty of using a placebo test for the hyperventilatory or breath-holding test makes their results weaker. The blindness of the raters to the test used for each patient increases the strength of our results but we recognize it was difficult to assure a complete blindness since some patients talked about the test while being evaluated. During the tests the raters stayed outside the room.

Since the tests used in our trial are very different in their methodology (hyperventilation vs breath-holding) we do not think that the fact that there was a fixed order in the test presentation interfered with the results. This

would only happen if the patients could be trained for the second test. It is difficult to separate the biological and psychological factors influencing the results observed.

Several studies do not support the idea that hyperventilation elicits panic attacks (5,24). It may be that hyperventilation is a

Table 2. Subjective anxiety levels just before and after hyperventilating in the hyperventilation-sensitive panic attack group (HPA) vs the breath-holding-sensitive panic attack group (BHPA) just before and after breath holding.

Self-rating	HPA (N = 24)	BHPA (N = 20)
SUDS before	2.4 ± 1.7	2.3 ± 1.8
SUDS after	7.1 ± 2.5	6.9 ± 3.0

Data are reported as means ± SD. SUDS = Subjective Units of Disturbance Scale. Data were analyzed by two-way ANOVA. Group by time interaction:  $F = 4.56$ ,  $d.f. = 1.43$ ,  $P = 0.878$ . Effect of time:  $F = 31.25$ ,  $d.f. = 1.43$ ,  $P < 0.001$  (Fisher protected least significant difference: HPA vs BHPA,  $P = 0.534$ ).

Table 3. Frequency of panic attack symptoms in the hyperventilation-sensitive panic attack group (HPA) vs the breath-holding-sensitive panic attack group (BHPA).

Symptoms	HPA (N = 24)	BHPA (N = 20)
Fear of dying	22 (91.7)	19 (95)
Chest pain/discomfort	17 (70.8)	19 (95)
Shortness of breath	18 (75.0)	18 (90)
Paresthesias	16 (66.7)	17 (85)
Feelings of choking	15 (62.5)	17 (85)
Dizziness/ lightheadedness	14 (58.3)	12 (60)
Depersonalization/ derealization	11 (45.8)	12 (60)
Losing control/going crazy	12 (50.0)	11 (55)
Chills/hot flushes	9 (37.5)	10 (50)
Nausea/abdominal distress	8 (33.3)	9 (45)
Palpitations	8 (33.3)	9 (45)
Sweating	9 (37.5)	7 (35)
Trembling/shaking	7 (29.2)	8 (40)

Data are reported as number of patients (% of total).  $P > 0.05$  for  $\chi^2$  analysis of all symptoms.



consequence of panic attacks in hyperventilation-predisposed individuals (10,24). A variety of studies have shown that differences between individuals with and without PD in measurements of panic during hyperventilation challenges are considerably lower than those observed in CO<sub>2</sub> challenges (25,26). In addition, PD individuals appeared to be less compliant with the hyperventilation instructions than the other groups (26). PD patients are not a homogenous group. Clinical and laboratory tests can find subgroups with importance for theoretical and therapeutic considerations.

Voluntary breath holding was not previously found to be a suitable test to measure suffocation alarm threshold in some PD studies. Asmundson and Stein (27) compared the duration of breath holding in PD (N = 23), generalized social phobia (N = 10), and healthy subjects (N = 26). The PD group had a significantly shorter breath-holding duration than either comparison group but the groups did not differ in terms of physiological response. Roth et al. (28) studied a 30-s breath-holding test repeated 12 times and also did not find any physiological support for a sensitive suffocation alarm system in PD. van der Does (20) investigated voluntary breath holding in PD patients, mood disorder patients and normal controls and detected no difference in mean breath-holding durations. Zandbergen et al. (29) tested breath holding in a small sample of PD patients (N = 14), in patients with other anxiety disorders (N = 14), and in 14 healthy controls. Apnea times appeared to be longer in the control group. No differences were found with respect to increase in anxiety during breath holding. Perhaps our results were different because we used more restricted inclusion and exclusion criteria, the PD pa-

tients were severe ones with current spontaneous panic attacks, we used clinical scales and criteria instead of just physiological measures, and our criteria for panic attack were clearly specified.

Perhaps the respiratory PD subtype could be divided into at least two groups: 1) hyperventilation-sensitive subjects and 2) suffocation false alarm-sensitive subjects. These groups would be sensitive to a respiratory challenge but the mechanism for a panic attack would be the low CO<sub>2</sub> and a decrease in basilar arterial blood flow (30) for the former group, and the increase in CO<sub>2</sub> for the latter (1).

Klein's "suffocation false alarm" mechanism (1) emphasizes the increase in CO<sub>2</sub> as a stimulus for the panic symptoms. The finding opposite to this mechanism, i.e., that hyperventilation induces panic attacks in PD if the chemoreceptors are more sensitive to the hypercapnic rise, would indicate that subjects should be less likely to panic when they become hypocapnic. Perhaps the explanation lies in the systemic alkalosis produced by hyperventilation similar to the lactate infusion test. In support of this idea is a study by Stewart et al. (31), in which regional cerebral blood flow was measured during rest and immediately after a lactate infusion with xenon-133 single-photon emission computed tomography.

Our study compared the clinical features of PD patients sensitive to one of two respiratory methods indicating panic attacks, i.e., hyperventilation and breath holding. HPA patients had a higher family prevalence of the disorder and a later onset of the disease compared to BHPA patients. This suggests that these two groups may represent subtypes of the PD.

## References

- Klein DF (1996). Panic disorder and agoraphobia: hypothesis hot-house. *Journal of Clinical Psychiatry*, 57: 21-27.
- Gorman JM, Kent JM, Sullivan GM & Coplan JD (2000). Neuroanatomical hypothesis of panic disorder, revised. *American Journal of Psychiatry*, 157: 493-505.
- Gorman JM, Papp LA, Coplan JD, Martinez JM, Lennon S, Goetz RR, Ross D & Klein DF (1994). Anxiogenic effects of CO<sub>2</sub> and hyperventilation in patients with panic disorder. *American Journal of Psychiatry*, 151: 547-553.
- 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. *American Journal of Psychiatry*, 154: 1557-1565.
- Papp LA, Klein DF & Gorman JM (1993). Carbon dioxide hypersensitivity, hyperventilation and panic disorder. *American Journal of Psychiatry*, 150: 1149-1157.
- Bataglia M & Perna G (1995). The 35% CO<sub>2</sub> challenge in panic disorder: optimization by receiver operating characteristic (roc) analysis. *Journal of Psychiatric Research*, 29: 111-119.
- Rapee R, Brown T, Antony M & Barlow D (1992). Response to hyperventilation and inhalation of 5.5% carbon dioxide-enriched air across the DSM-III-R anxiety disorders. *Journal of Abnormal Psychology*, 101: 538-552.
- Holt PE & Andrews G (1989). Hyperventilation and anxiety in panic disorder, social phobia, GAD and normal controls. *Behaviour Research and Therapy*, 27: 453-460.
- 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.
- Perna G, Cocchi S, Bertani A, Arancio C & Bellodi L (1995). Sensitivity to 35% CO<sub>2</sub> in healthy first-degree relatives of patients with panic disorder. *American Journal of Psychiatry*, 152: 623-625.
- Papp LA, Klein DF & Gorman JM (1998). Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. In: Bellodi L & Perna G (Editors), *The Panic Respiration Connection*. Medical Media, Milan, Italy.
- Nardi AE, Valença AM, Nascimento I & Zin WA (2001). Hyperventilation challenge test in panic disorder and depression with panic attacks. *Psychiatry Research*, 105: 57-65.
- Nardi AE, Valença AM, Nascimento I & Zin WA (2002). Panic disorder and obsessive compulsive disorder in a hyperventilation challenge test. *Journal of Affective Disorders*, 68: 335-340.
- Nardi AE, Valença AM, Nascimento I, Mezzasalma MA, Lopes FL & Zin WA (2000). Hyperventilation in panic disorder patients and healthy first-degree relatives. *Brazilian Journal of Medical and Biological Research*, 33: 1317-1323.
- Nardi AE, Valença AM, Nascimento I, Mezzasalma MA & Zin WA (2001). Hyperventilation in panic disorder and social phobia. *Psychopathology*, 34: 123-127.
- Nardi AE, Nascimento I, Valença AM, Lopes FL, Zin WA, Mezzasalma MA & Versiani M (2002). A breath-holding challenge in panic disorder patients, their healthy first-degree relatives, and normal controls. *Respiration Physiology and Neurobiology*, 133: 43-47.
- First MB, Spitzer RL, Gibbon M & Williams JBM (1997). *Structured Clinical Interview Diagnostic (SCID) for DSM-IV Axis I Disorders - Clinician Version (SCID-CV)*. American Psychiatric Press, Washington, DC, USA.
- American Psychiatric Association (1994). *Diagnostic and Statistical Manual for Mental Disorders*. 4th edn. DSM-IV. American Psychiatric Press, Washington, DC, USA.
- Bech P, Kastrup M & Rafaelsen OJ (1986). Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia with corresponding DSM III syndromes. *Acta Psychiatrica Scandinavica*, 73: 1-37.
- van der Does AJW (1997). Voluntary breath holding: not a suitable probe of the suffocation alarm in PD. *Behaviour Research and Therapy*, 35: 779-784.
- Briggs AC, Stretch DD & Brandon S (1993). Subtyping of panic disorder by symptom profile. *British Journal of Psychiatry*, 163: 201-209.
- Bandelow B, Amering M, Benkert O, Marks I, Nardi AE, Osterheider M, Tannock C, Tremper J & Versiani M (1996). Cardio-respiratory and other symptom clusters in panic disorder. *Anxiety*, 2: 99-101.
- Salkovskis PM, Jones DO & Clark DM (1986). Respiratory control in treatment of panic attacks: replication and extension with concurrent measurement of behaviour and PCO<sub>2</sub>. *British Journal of Psychiatry*, 148: 526-532.
- Bass C (1997). Hyperventilation syndrome: a chimera? *Journal of Psychosomatic Research*, 42: 421-426.
- Humble M (1987). Aetiology and mechanisms of anxiety disorders. *Acta Psychiatrica Scandinavica*, 76: 15-30.
- Antony MM, Brown TA & Barlow DH (1997). Response to hyperventilation and 5.5% CO<sub>2</sub> inhalation of subjects with types of specific phobia, panic disorder, or no mental disorder. *American Journal of Psychiatry*, 154: 1089-1095.
- Asmundson GJ & Stein MB (1994). Triggering the false suffocation alarm in panic disorder patients by using a voluntary breath-holding procedure. *American Journal of Psychiatry*, 151: 264-266.
- Roth WT, Wilhelm FH & Trabert W (1998). Voluntary breath holding in panic and generalized anxiety disorders. *Psychosomatic Medicine*, 60: 671-679.
- Zandbergen J, Strahm M, Pols H & Griez E (1992). Breath-holding in panic disorder. *Comprehensive Psychiatry*, 33: 47-51.
- Ball S & Shekhar A (1997). Basilar artery response to hyperventilation in panic disorder. *American Journal of Psychiatry*, 154: 1603-1604.
- Stewart RS, Devous Sr MD, Rush AJ, Lane L & Bonte FJ (1988). Cerebral blood flow changes during sodium-lactate-induced panic attacks. *American Journal of Psychiatry*, 145: 442-449.