Available online at www.sciencedirect.com
SCIENCE DIRECT®
PERGAMON
Journal of Behavior Therapy and Experimental Psychiatry 34 (2003) 161–170
JOURNAL OF behavior therapy and experimental psychiatry
www.elsevier.com/locate/jbtep

Emotional responding to hyperventilation as a predictor of agoraphobia status among individuals suffering from panic disorder

Michael J. Telch[a,*], Kristine Jacquin[b], Jasper A.J. Smits[a], Mark B. Powers[a]

[a] *Laboratory for the Study of Anxiety Disorders, Department of Psychology, University of Texas at Austin, Mezes 330, Mail Stop B3800, Austin, TX 78712, USA*
[b] *Department of Psychology, Mississippi State University, USA*

Received 5 July 2002; received in revised form 6 December 2002; accepted 6 May 2003

Abstract

Some data suggest that panic patients with extensive agoraphobia (PDA) display more intense respiratory distress during their panic attacks than Panic disorder (PD) patients. However, no studies have determined if PDA patients also show heightened sensitivity to a respiratory challenge compared to PD patients. The current study examined the differential emotional responding to hyperventilation among PDA patients, PD patients, and a non-clinical group with a history of panic attacks. Response to hyperventilation challenge did not distinguish non-clinical panickers from panic patients; however, behavioral tolerance to hyperventilation challenge significantly predicted agoraphobia status among panic disorder patients, even after controlling for demographic and clinical status variables.

Keywords: Panic disorder; Agoraphobia; Hyperventilation; Respiration; Anxiety sensitivity; Challenge test

1. Introduction

Challenging patients in the laboratory has been a widely used tool in the study of panic disorder (PD). There is now ample evidence demonstrating that compared to normal controls, PD patients display heightened physiologic activation, marked rise

*Corresponding author. Tel.: +1-512-471-3393; fax: +1-512-471-6175.
E-mail address: telch@forum.utexas.edu (M.J. Telch).

0005-7916/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0005-7916(03)00037-5

in fear, and increased probability of panic in response to voluntary hyperventilation (Beck & Scott, 1988; Gorman et al., 1984, 1988, 1994; Holt & Andrews, 1989a, b; Nardi, Valenca, Nascimento, Mezzasalma, & Zin, 1999, 2001; Papp et al., 1997), inhalation of 5% CO_2 (Gorman et al., 1984, 1988, 1994; Papp et al., 1997; Woods, Charney, Goodman, & Heninger, 1988), 7% CO_2 (Gorman et al., 1994; Papp et al., 1997), and 35% CO_2 (Gorman et al., 1990; Griez, Lousberg, van den Hout, & van der Molen, 1987; Papp et al., 1993; Perna et al., 1995, 1994; Perna, Gabriele, Caldirola, & Bellodi, 1995). Moreover, PD sufferers show greater sensitivity to 5% and 35% CO_2 than patients with obsessive compulsive disorder (Griez, de Loof, Pols, Zandbergen, & Lousberg, 1990; Perna, Bertani, Arancio, Ronchi, & Bellodi, 1995), generalized anxiety disorder (Perna, Bussi, Allevi, & Bellodi, 1999; Verburg, Griez, Meijer, & Pols, 1995) or depression (Kent et al., 2001; Perna, Barbini, Cocchi, Bertani, & Gasperini, 1995) and greater sensitivity to hyperventilation challenges compared to those with generalized anxiety disorder, or social phobia (Holt & Andrews, 1989b; Rapee, Brown, Antony, & Barlow, 1992). Based on these findings, it has been suggested that respiratory abnormalities play a central role in the pathogenesis of panic disorder (Klein, 1993).

Despite the plethora of respiratory challenge studies, none to our knowledge have examined differential emotional responding to hyperventilation among panic patients with and without extensive agoraphobic avoidance. When present in panic disorder, agoraphobia is associated with markedly greater disruption in quality of life (de Jong & Bouman, 1995), significantly higher rates of comorbid depression (Goisman et al., 1994), substance abuse (Rapee & Medoro, 1994), and a less favorable response to both pharmacologic and cognitive-behavioral treatment (Goisman et al., 1994; Keller et al., 1994). Although panic patients with and without agoraphobia do not differ on panic attack frequency (Cox, Endler, & Swinson, 1995; Craske & Barlow, 1988; Rapee & Murrell, 1988; Telch, Brouillard, Telch, Agras, & Taylor, 1989), there are some data suggesting that panic patients with agoraphobia may display more intense respiratory distress such as faintness or dizziness during their panic attacks (de Jong & Bouman, 1995; Noyes, Clancy, Garvey, & Anderson, 1987; Telch et al., 1989).

The overall aim of the present investigation was to examine the role of respiratory sensitivity in panic disorder and agoraphobia by comparing emotional responding to voluntary hyperventilation challenge among three panic groups: non-patients with current panic attacks (non-clinical panickers (NP)), patients with PD but minimal or no agoraphobia, and patients with PD plus moderate to severe agoraphobia. Several specific questions were addressed: (a) Do patients with PD (with or without agoraphobia) display greater anxious responding to a respiratory challenge compared to NP? (b) Do patients with PD with significant agoraphobia display heightened emotional responding relative to PD patients with minimal or no agoraphobia? and (c) Do measures of emotional sensitivity to hyperventilation challenge predict patients' clinical status after controlling for clinical and demographic differences. Similarly, do indices of respiratory sensitivity predict agoraphobia status, even after controlling for differences in demographic and clinical characteristics?

2. Method

2.1. Participants

Fifty-nine patients with DSM-III-R-diagnosed PD with moderate or severe agoraphobia (PDA), 46 patients with DSM-III-R-diagnosed PD and 44 NP participated in this study. All PD patients were referred to our laboratory from physicians and mental health professionals in the Austin area as part of a larger PD treatment outcome study (Telch et al., 1993). NP were drawn from approximately 900 students in introductory psychology classes at the University of Texas at Austin. Diagnoses were established using the Structured Clinical Interview for DSM-III-R (American Psychiatric Association, 1987). Although some patients met for more than one Axis I diagnosis, PD with or without agoraphobia was the principal diagnosis for all clinical cases. Participants in the NP group had experienced at least one unexpected panic attack but did not meet DSM-III-R criteria for current or past PD. Demographic characteristics of the participants in each of the three groups are presented in Table 1.

2.2. Procedures

Participants were interviewed using the Anxiety Disorders module of the SCID-NP (Spitzer, Williams, Gibbon, & First, 1992) after which they completed the following rating scales: Anxiety Sensitivity Index (Peterson & Reiss, 1987), Beck Anxiety Inventory (Beck & Steer, 1990), Mobility Inventory, (Chambless, Caputo, Jasin, Gracely, & Williams, 1985), Beck Depression Inventory Beck (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and Beck Hopelessness Scale (Beck, Weissman, Lester, & Trexler, 1974). They also indicated frequency and severity of panic attacks in the past 30 days. Participants then underwent the hyperventilation

Table 1
Demographic and clinical characteristics of PD patients, PD patients with agoraphobia, and NP

Characteristic	NP ($N=44$)		PD ($N=46$)		PDA ($N=59$)	
	Mean	SD	Mean	SD	Mean	SD
Age	19.59	2.71	37.20	11.03	33.54	8.41
	N	%	*N*	%	*N*	%
Gender						
Men	18	41	16	35	10	17
Women	26	59	30	65	49	83
Comorbid anxiety diagnoses						
Social phobia	2	5	7	15	11	19
Obsessive-compulsive disorder	0	0	1	2	5	8
Generalized anxiety disorder	1	2	7	15	7	12
Specific phobia	0	0	7	15	13	22

challenge test. During this test, participants were instructed to take full vital capacity breaths every 2 s. Participants' rate of breathing was paced using a taped female voice announcing the words "inhale" and "exhale." Prior to starting the rapid breathing procedure, a female experimenter modeled the procedure for the participant and answered any questions. Participants were instructed to perform the rapid breathing procedure for as long as they could. Although the rapid breathing procedure was stopped after 120 s, participants were not informed of this limit. This allowed us to use hyperventilation duration as a behavioral index of emotional response to the challenge.

Immediately after cessation of rapid breathing, participants completed a brief rating form indicating the severity of 16 symptoms experienced during the hyperventilation challenge. Each symptom was rated on an 8-point Likert scale ranging from 0 (not at all) to 3 (severe). The total score served as an index of symptom severity. In addition, participants rated their peak fear *during* the hyperventilation challenge from 1 (none) to 10 (extreme panic). The duration of hyperventilation (in seconds) was recorded and served as a behavioral index of anxious responding. Written informed consent was obtained from all participants after full explanation of study procedures. The study was approved by the institutional review board of the University of Texas at Austin.

3. Data analyses

Differences between patients (PD and PDA groups combined) and non-patients (NCP group) were examined using a priori multivariate contrasts. Two separate analyses were performed—one for the cluster of clinical status measures (i.e., panic frequency, anxiety sensitivity, agoraphobia, anxiety, depression, and hopelessness), and one for the cluster of hyperventilation challenge indices (i.e., symptom severity, peak fear, and hyperventilation duration). A similar strategy was used to compare the two patient groups (PDs vs. PDAs). We also performed hierarchical logistic regression analyses to determine if response to hyperventilation challenge predicted participants' clinical status (patients vs. NP) after controlling for differences in demographic and clinical variables. Similarly, we conducted a second similar logistic regression analysis to determine if the hyperventilation indices predicted agoraphobia status (PD vs. PDA patients) after controlling for differences in demographic and clinical variables. In each of these analyses, demographic and clinical measures were entered in Block 1, followed by the three hyperventilation indices in Block 2.

4. Results

Sixty non-clinical participants entered the study. Ten were excluded because they met DSM-III-R criteria for past (nine participants) or current (one participant) PD. Six additional participants refused the hyperventilation challenge and were thus excluded. There were no disagreements on principal and secondary diagnoses for the

clinical participants. The participants in the NCP group were significantly younger than the participants in the two clinical groups ($F = 107.64$, df = 1, 147, $p < 0.001$). There was also a higher proportion of women in the PDA group compared to either the PD group or the NCP group ($\chi^2 = 4.41$, df = 1, $p < 0.05$). Demographic and clinical characteristics are presented in Table 1.

4.1. Clinical measures

Means, standard deviations, and planned contrast analyses for the cluster of clinical measures are presented in Table 2. Overall, the two clinical PD groups scored significantly higher (greater dysfunction) than the non-clinical panic group (Wilks' Lambda = 18.22, df = 8, 139, $p < 0.001$). Follow-up univariate contrasts yielded significant differences on all individual clinical measures (see Table 2), with the exception of the BHS. As expected, compared to PDs, PDAs reported significantly more agoraphobic severity on the Mobility Inventory (MI-alone: $F = 161.70$, df = 1, 103, $p < 0.001$; MI-accompanied: $F = 42.65$, df = 1, 103, $p < 0.001$). PDAs also scored significantly higher than PDs on the Beck Anxiety Inventory ($F = 8.91$, df = 1, 103, $p < 0.05$). The two clinical groups did not differ on any of the other clinical measures.

4.2. Emotional response to hyperventilation

Means, standard deviations, and planned contrast analyses for hyperventilation indices are presented in Table 3. Overall, the two clinical PD groups showed greater anxious responding to hyperventilation than the non-clinical panic group, even after controlling for baseline anxiety as indexed by the BAI (Wilks' Lambda = 6.45, df = 3,

Table 2
Means, standard deviations and planned multivariate and univariate contrasts for the major clinical variables

Clinical variable	NP ($N = 44$)		PD ($N = 46$)		PDA ($N = 59$)		NP vs. PD + PDA	PD vs. PDA
	Mean	SD	Mean	SD	Mean	SD	*F* value	*F* value
Panic frequency	0.84	1.20	8.07	16.14	10.93	15.44	13.78[a]	0.86
Panic severity	15.68	8.49	50.26	25.05	60.19	24.87	103.49[a]	4.09
ASI	18.98	8.93	32.85	11.16	36.49	9.87	80.06[a]	3.14
BAI	12.27	12.53	21.63	9.16	27.27	10.64	42.15[a]	8.19[b]
MI-Alone	1.49	0.46	1.77	0.47	3.25	0.67	57.50[a]	161.70[a]
MI-Accompanied	1.15	0.22	1.49	0.37	2.29	0.77	47.66[a]	42.65[a]
BDI	8.88	6.83	13.76	8.13	16.25	8.96	17.99[a]	2.16
BHS	4.25	3.61	6.33	4.69	6.00	4.23	6.43	0.14

Note: ASI = Anxiety Sensitivity Index; BAI = Beck Anxiety Inventory; MI-Alone = Mobility Inventory (Unaccompanied); MI-Acc. = Mobility Inventory (Accompanied); BDI = Beck Depression Inventory; BHS = Beck Hopelessness Scale.

[a] Significant at the 0.01 level with Bonferroni correction.

[b] Significant at the 0.05 level with Bonferroni correction.

Table 3
Means, standard deviations and planned multivariate and univariate contrasts for the hyperventilation indices

Hyperventilation index	NP ($N=44$)		PD ($N=45$)		PDA ($N=59$)		NP vs. PD + PDA	PD vs. PDA
	Mean	SD	Mean	SD	Mean	SD	F value	F value
Physical SX intensity (0–48)	10.72	8.47	11.80	9.97	16.47	9.34	0.01	2.24
Peak fear (1–10)	2.70	2.00	3.75	2.06	4.74	1.78	9.30[a]	3.29
Duration (0–120)	119.77	1.51	115.18	14.58	88.00	37.40	8.00[a]	15.74[a]

[a] Significant at the 0.01 level Bonferroni correction after controlling for baseline BAI.

139, $p<0.001$). Follow-up univariate contrasts revealed significant differences in peak fear during hyperventilation ($F=9.30$, df = 1, 141, $p<0.01$) and hyperventilation duration ($F=8.00$, df = 1, 141, $p<0.01$). The groups did not differ on the intensity of symptoms reported during hyperventilation.

Comparisons between the two clinical groups showed enhanced anxious responding to hyperventilation among PDA patients (Wilks' Lambda = 5.56, df = 3, 96, $p<0.01$). Follow-up contrasts showed that compared to PDs, PDAs showed significantly less tolerance as indexed by hyperventilation duration ($F=15.73$, df = 1, 99, $p<0.001$). No differences were observed for symptom intensity or peak fear reported during hyperventilation.

4.3. Predicting patient status and level of agoraphobia

Results of the hierarchical logistic regression analyses revealed that level of emotional responding to hyperventilation did not predict caseness after controlling for clinical and demographic differences. Duration of hyperventilation significantly predicted agoraphobia status among PD patients, even after controlling for differences in demographic and clinical characteristics (Wald $\chi^2=8.78$, df = 1, $p<0.05$).

5. Discussion

To our knowledge, these findings represent the first examination of response to respiratory challenge comparing individuals displaying varying levels of panic psychopathology (i.e., non-clinical panic, PD without agoraphobia, and PD with agoraphobia). As expected, results revealed that regardless of agoraphobia status, clinical participants with PD exhibited greater emotional sensitivity to voluntary hyperventilation challenge relative to non-clinical participants with panic attacks. This heightened sensitivity was observed on both peak fear and behavioral tolerance, but not on physical symptom severity. It should be noted, however, that our non-clinical panic sample showed significantly less pathology than the two PD patient

groups on a number of clinical measures (e.g., depression, anxiety, and panic symptom severity, anxiety sensitivity). This latter finding raises the question as to whether the observed enhanced responding to hyperventilation simply represents greater levels of general psychopathology. To address this issue, we examined the incremental validity of the hyperventilation sensitivity measures in predicting clinical status (i.e., patients vs. NP) after controlling for differences on the various clinical measures. The results provided no evidence that emotional sensitivity to hyperventilation challenge predicted caseness beyond other clinical indices of severity.

The failure to find differences in the intensity of hyperventilation-induced physical symptoms between the NP and the two patient groups suggests that it is the affective reaction to hyperventilation—not participants' physical reaction that best distinguishes patients from non-patients. These data are quite consistent with the large body of evidence suggesting that PD patients exhibit heightened fear of somatic sensations (i.e., anxiety sensitivity) relative to controls (Barlow et al., 1985; Chambless & Gracely, 1989; Clark et al., 1997; Taylor, Koch, & McNally, 1992).

Does sensitivity to respiratory challenge differ among panic patients with and without agoraphobia? Our findings revealed that panic patients with agoraphobia showed heightened sensitivity to challenge relative to the non-agoraphobic patient sample. The heightened sensitivity was observed specifically for behavioral tolerance. To examine whether the observed hypersensitivity to challenge was simply a consequence of the greater psychopathology observed among the agoraphobic sample, we again tested the incremental validity of the hyperventilation challenge measures in predicting agoraphobia status after controlling for differences in demographic and clinical variables. Our findings revealed that sensitivity to hyperventilation predicted agoraphobia status even after controlling for these other variables.

We can only speculate as to the factors accounting for the enhanced sensitivity to respiratory challenge observed among the agoraphobic group. First, we considered the hypothesis that the observed sensitivity was simply a function of a general heightened fear of somatic sensations among the agoraphobics. However, this hypothesis was not supported by the finding that the increased sensitivity to voluntary hyperventilation observed for the agoraphobics remained significant after statistically controlling for the effects of anxiety sensitivity. We also considered the possibility that PD patients who go on to develop extensive agoraphobia are more likely to represent a distinct subtype of PD characterized by neurophysiologic dysregulation similar to that put forth by Klein in his suffocation theory of PD (Klein 1993). However, this hypothesis would predict that those patients should also exhibit heightened physical symptoms in response to hyperventilation. We found no evidence of increased physical symptoms among the agoraphobic group.

It is also possible that the enhanced sensitivity to hyperventilation among the agoraphobics is a function of a more general personality predisposition characterized by low tolerance of fear. This hypothesis is consistent with our finding that hyperventilation tolerance, as indexed by the duration of voluntary hyperventilation, was the most potent discriminator between panic patients with and without agoraphobia.

Several limitations of the study deserve comment. First, our study did not collect physiologic data such as expired air CO_2, which might have revealed important differences between groups. Most importantly, the cross-sectional nature of the study precludes causal inferences regarding the role of emotional sensitivity to respiratory challenge in the development of PD and agoraphobia. Longitudinal studies are needed to address the etiologic significance of our findings.

Acknowledgements

This research was funded by National Institute of Mental Health Grant MH74-600-203.

References

American Psychiatric Association (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., revised). Washington, DC: Author.

Barlow, D. H., Vermilyea, J., Blanchard, E. B., Vermilyea, B. B., Di Nardo, P. A., & Cerny, J. A. (1985). The phenomenon of panic. *Journal of Abnormal Psychology*, *94*(3), 320–328.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–571.

Beck, A. T., Weissman, A., Lester, D., & Trexler, L. (1974). The measurement of pessimism: The Hopelessness Scale. *Journal of Consulting & Clinical Psychology*, *42*, 861–886.

Beck, A. T., & Steer, R. A. (1990). *Manual for the Beck Anxiety Inventory*. San Antonio, TX: Psychological Corporation.

Beck, J. G., & Scott, S. K. (1988). Physiological and symptom responses to hyperventilation: A comparison of frequent and infrequent panickers. *Journal of Psychopathology & Behavioral Assessment*, *10*, 117–127.

Chambless, D. L., Caputo, G. C., Jasin, S. E., Gracely, E. J., & Williams, C. (1985). The mobility inventory for agoraphobia. *Behavior Research & Therapy*, *23*(1), 35–44.

Chambless, D. L., & Gracely, E. J. (1989). Fear of fear and the anxiety disorders. *Cognitive Therapy & Research*, *13*, 9–20.

Clark, D. M., Salkovskis, P. M., Ost, L. G., Breitholtz, E., Koehler, K. A., Westling, B. E., Jeavons, A., & Gelder, M. (1997). Misinterpretation of body sensations in panic disorder. *Journal of Consulting & Clinical Psychology*, *65*(2), 203–213.

Cox, B. J., Endler, N. S., & Swinson, R. P. (1995). An examination of levels of agoraphobic severity in panic disorder. *Behaviour Research & Therapy*, *33*, 57–62.

Craske, M. G., & Barlow, D. H. (1988). A review of the relationship between panic and avoidance. *Clinical Psychology Review*, *8*, 667–685.

de Jong, G. M., & Bouman, T. K. (1995). Panic disorder: A baseline period. Predictability of agoraphobic avoidance behavior. *Journal of Anxiety Disorders*, *9*, 185–199.

Goisman, R. M., Warshaw, M. G., Peterson, L. G., Rogers, M. P., Cuneo, P., Hunt, M. F., Tomlin-Albanese, J. M., Kazim, A., Gollan, J. K., & Epstein-Kaye, T., et al. (1994). Panic, agoraphobia, and panic disorder with agoraphobia. Data from a multicenter anxiety disorders study. *Journal of Nervous and Mental Disease*, *182*(2), 72–79.

Gorman, J. M., Askanazi, J., Liebowitz, M. R., Fyer, A. J., Stein, J., Kinney, J. M., & Klein, D. F. (1984). Response to hyperventilation in a group of patients with panic disorder. *American Journal of Psychiatry*, *141*(7), 857–861.

Gorman, J. M., Fyer, M. R., Goetz, R., Askanazi, J., Liebowitz, M. R., Fyer, A. J., Kinney, J., & Klein, D. F. (1988). Ventilatory physiology of patients with panic disorder. *Archives of General Psychiatry*, *45*(1), 31–39.

Gorman, J. M., Papp, L. A., Martinez, J., Goetz, R. R., Hollander, E., Liebowitz, M. R., & Jordan, F. (1990). High-dose carbon dioxide challenge test in anxiety disorder patients. *Biological Psychiatry*, *28*(9), 743–757.

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

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*(2), 193–199.

Griez, E. J., Lousberg, H., van den Hout, M. A., & van der Molen, G. M. (1987). CO_2 vulnerability in panic disorder. *Psychiatry Research*, *20*(2), 87–95.

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

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

Keller, M. B., Yonkers, K. A., Warshaw, M. G., Pratt, L. A., Gollan, J. K., Massion, A. O., White, K., Swartz, A. R., Reich, J., & Lavori, P. W. (1994). Remission and relapse in participants with panic disorder and panic with agoraphobia: A prospective short-interval naturalistic follow-up. *Journal of Nervous and Mental Disease*, *182*(5), 290–296.

Kent, J. M., Papp, L. A., Martinez, J. M., Browne, S. T., Coplan, J. D., Klein, D. F., & Gorman, J. M. (2001). Specificity of panic response to CO(2) inhalation in panic disorder: A comparison with major depression and premenstrual dysphoric disorder. *American Journal of Psychiatry*, *158*(1), 58–67.

Klein, D. F. (1993). False suffocation alarms, spontaneous panics, and related conditions: An integrative hypothesis. *Archives of General Psychiatry*, *50*, 306–317.

Nardi, A. E., Valenca, A. M., Nascimento, I., Mezzasalma, M. A., & Zin, W. (1999). Panic disorder and hyperventilation. *Arquivos Neuro-Psiquiatria*, *57*(4), 932–936.

Nardi, A. E., Valenca, A. M., Nascimento, I., Mezzasalma, M. A., & Zin, W. A. (2001). Hyperventilation in panic disorder and social phobia. *Psychopathology*, *34*(3), 123–127.

Noyes, R., Clancy, J., Garvey, M. J., & Anderson, D. J. (1987). Is agoraphobia a variant of panic disorder or a separate illness? *Journal of Anxiety Disorders*, *1*, 3–13.

Papp, L. A., Klein, D. F., Martinez, J., Schneier, F., Cole, R., Liebowitz, M. R., Hollander, E., Fyer, A. J., Jordan, F., & Gorman, J. M. (1993). Diagnostic and substance specificity of carbon-dioxide-induced panic. *American Journal of Psychiatry*, *150*, 250–257.

Papp, L. A., Martinez, J. M., Klein, D. F., Coplan, J. D., Norman, R. G., Cole, R., de Jesus, M. J., Ross, D., Goetz, R., & Gorman, J. M. (1997). Respiratory psychophysiology of panic disorder: Three respiratory challenges in 98 participants. *American Journal of Psychiatry*, *154*(11), 1557–1565.

Perna, G., Barbini, B., Cocchi, S., Bertani, A., & Gasperini, M. (1995). 35% CO_2 challenge in panic and mood disorders. *Journal of Affective Disorders*, *33*(3), 189–194.

Perna, G., Barbini, B., Cocchi, S., Bertani, A., & Gasperini, M. (1995). 35% CO-sub-2 challenge in panic and mood disorders. *Journal of Affective Disorders*, *33*, 189–194.

Perna, G., Battaglia, M., Garberi, A., Cinzia, A., Bertani, A., & Bellodi, L. (1994). Carbon dioxide/oxygen challenge test in panic disorder. *Psychiatry Research*, *52*, 159–171.

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. *American Journal of Psychiatry*, *152*(1), 85–89.

Perna, G., Bussi, R., Allevi, L., & Bellodi, L. (1999). Sensitivity to 35% carbon dioxide in patients with generalized anxiety disorder. *Journal of Clinical Psychiatry*, *60*(6), 379–384.

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

Peterson, R. A., & Reiss, S. (1987). *Anxiety Sensitivity Index*. Palos Heights, IL: International Diagnostic Systems.

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

Rapee, R. M., & Medoro, L. (1994). Fear of physical sensations and trait anxiety as mediators of the response to hyperventilation in nonclinical participants. *Journal of Abnormal Psychology*, *103*(4), 693–699.

Rapee, R. M., & Murrell, E. (1988). Predictors of agoraphobic avoidance. *Journal of Anxiety Disorders*, *2*, 203–217.

Spitzer, R. L., Williams, J. B., Gibbon, M., & First, M. B. (1992). The structured clinical interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of General Psychiatry*, *49*(8), 624–629.

Taylor, S., Koch, W. J., & McNally, R. J. (1992). How does anxiety sensitivity vary across the anxiety disorders? *Journal of Anxiety Disorders*, *6*, 249–259.

Telch, M. J., Brouillard, M., Telch, C. F., Agras, W. S., & Taylor, C. B. (1989). Role of cognitive appraisal in panic-related avoidance. *Behaviour Research & Therapy*, *27*(4), 373–383.

Telch, M. J., Lucas, J. A., Schmidt, N. B., Hanna, H. H., Jaimez, T. L., & Lucas, R. A. (1993). Group cognitive-behavioral treatment of panic disorder. *Behaviour Research & Therapy*, *31*(3), 279–287.

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

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