Sensitivity to 35% Carbon Dioxide in Patients With Generalized Anxiety Disorder

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Background: Panic disorder and generalized anxiety disorder (GAD) are both characterized by severe anxiety, but there is evidence that indicates a qualitative difference between these 2 anxiety disorders. To investigate the specificity of the association between carbon dioxide (CO_2) hypersensitivity and panic disorder and the possible relationships between panic disorder and GAD, the responses to inhalation of a gas mixture of 35% CO_2 and 65% oxygen (O_2) were assessed.

Method: Fifteen patients with panic disorder, 13 patients with GAD, and 10 patients with comorbid GAD and panic disorder according to a consensus diagnosis using Diagnostic Interview Schedule Version III-R (DIS-R) and DSM-IV criteria, and 12 healthy controls inhaled 2 vital capacities: 1 of 35% CO_2 and 1 of compressed air. A double-blind, randomized, crossover design was used.

Results: GAD patients showed reactions to 35% CO_2 that were similar to those of healthy controls and significantly weaker than that of panic disorder patients. Patients with comorbid panic disorder and GAD had anxiogenic reactions similar to those of subjects with panic disorder.

Conclusion: The results of the present study support the idea that panic disorder and GAD are separate disorders that have at least some differences in pathogenetic mechanisms and suggest that the 35% CO_2 test might be a valid tool for discriminating between these 2 disorders.

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The question whether generalized anxiety disorder (GAD) is a discrete syndrome or whether it might be the prodromal or residual phase of other diseases has been extensively discussed in the literature.[1–4] The question arose from the observation that GAD rarely occurs in isolation but has a very high rate of comorbidity with other diseases.[5,6] Since the publication of the Diagnostic and Statistical Manual for Mental Disorders, Third Edition (DSM-III),[7] GAD has been described as a discrete disorder separate from panic disorder, but claims regarding the distinction and the relationships between these 2 disorders remain controversial.

This discussion arose from studies showing that imipramine alleviated panic attacks, but not generalized anxiety, in patients with agoraphobia.[8] Although Klein's "pharmacological dissection"[8] has been remarkably fruitful, subsequent research has blurred this distinction. Benzodiazepines have been reported to be effective in patients with panic disorder,[9,10] and, moreover, imipramine has shown efficacy in the treatment of patients with GAD without panic attacks or depression.[11,12] In addition, selective serotonin reuptake inhibitors (SSRIs) effective in treating panic disorder are useful in treating GAD.[13,14]

Despite these pharmacologic similarities, a variety of data support the separation of these 2 disorders. GAD has a more gradual onset and, at least in clinical samples,[15–19] an earlier age at onset than panic disorder. Family and twin studies also seem to support the separation of panic disorder from GAD.[18,20–23] The activation of the autonomic nervous system is higher in patients with panic disorder than in those with GAD,[24–27] and patients with GAD show more arousal as manifested by increased vigilance.[27] Finally, unlike patients with panic disorder, those with GAD rarely panic in response to lactate infusion.[28]

Responses to laboratory challenges could help to clarify the relationships between these 2 disorders. Among the laboratory markers used to investigate the psychobiological mechanisms underlying panic disorder, carbon dioxide (CO_2) hypersensitivity is one of the most widely studied, and several studies have supported its role as a biological marker of panic disorder or at least of a panic-phobic spectrum of disorders. Several studies[29–32] have shown that patients with panic disorder are hypersensitive to 35% CO_2 inhalations, whereas normal con-

trols, without a familial susceptibility to panic disorder, showed normal sensitivity, and patients with anxiety disorders other than panic disorder had heterogeneous responses. Three studies[31,33,34] reported that patients with social phobia show stronger reactions to 35% CO_2 inhalations than do healthy controls, although only Caldirola et al.[34] found reactions similar to those of patients with panic disorder. All 3 studies examining 35% CO_2 sensitivity in patients with obsessive-compulsive disorder (OCD) showed no differences from healthy controls.[35–37] The single study examining 35% CO_2 sensitivity in subjects with simple phobias[38] reported that subjects with situational simple phobias were hypersensitive, whereas subjects with animal simple phobias showed normal sensitivity. The single study examining 35% CO_2 reactivity in GAD[39] investigated a small sample of subjects (N = 9) and reported that patients with panic disorder reacted to the 35% CO_2 challenge with higher levels of subjective anxiety than patients with GAD, while increases in panic symptoms scores were high in both groups of patients. The authors concluded that high levels of subjective anxiety response to the 35% CO_2 challenge are specific for panic disorder and that the vulnerability to the 35% CO_2 challenge in patients with GAD is similar to the vulnerability in healthy controls. Since CO_2 hypersensitivity has been linked to a specific psychobiological mechanism related to an abnormal suffocation alarm monitor, the different sensitivity to CO_2 reported could be the expression of different pathogenetic mechanisms.

In the present study, we have compared the reaction to 35% CO_2 inhalations in patients with panic disorder, patients with GAD, and patients with both panic disorder and GAD. The aims of this study were (1) to confirm the role of CO_2 hypersensitivity as a marker of specific type of anxiety and (2) to assess the possible effects of GAD codiagnosis on 35% CO_2 reactivity in patients with panic disorder. If patients with comorbid GAD and panic disorder were to show stronger or weaker reactions than those with panic disorder alone, a relationship between some of the pathogenetic mechanisms of GAD and panic disorder might be argued; a reaction to CO_2 for patients with comorbid GAD and panic disorder similar to that of patients with panic disorder alone would indicate an independence of the 2 disorders.

METHOD

Subjects

Four groups of subjects were included in this study: (1) 15 patients with panic disorder, (2) 13 patients with GAD, (3) 10 patients with comorbid GAD and panic disorder, and (4) 12 healthy controls. Subjects chosen for groups 1 and 2 were selected from patients who sought treatment consecutively over a 6-month period at the Anxiety Disorders Clinical and Research Unit of the Department of Neuropsychiatric Sciences at the San Raffaele Hospital, Milan, Italy; subjects in group 3 were recruited from the same unit over a longer period of time (12 months). Controls were recruited by advertisements placed around the University of Milan. Because previous studies reported the absence of a significant age effect on 35% CO_2 sensitivity,[32,33,40] groups were not age matched. All participants gave informed consent to the study after receiving a detailed explanation of the procedure.

Initial diagnoses were made using the Diagnostic Interview Schedule, Version III-R (DIS-R)[41]; interviewers were psychiatrists or residents in psychiatry trained in the use of the DIS-R interview. Data obtained were afterwards reanalyzed according to DSM-IV criteria,[42] and consensus diagnoses were made by 2 experienced psychiatrists blind to the results of the 35% CO_2 challenge. Controls had never fit any lifetime psychiatric diagnoses, according to the DIS-R, and had never experienced unexpected panic attacks. "Pure" GAD patients had never experienced unexpected panic attacks.

Exclusion criteria for all subjects were significant cardiocirculatory and respiratory disorders, personal or family history of cerebral aneurysm, significant hypertension (systolic blood pressure > 180 mm Hg, diastolic blood pressure > 100 mm Hg), pregnancy, or epilepsy, all determined through direct physical examination and careful collection of medical histories. Other exclusion criteria were, for all the patients, the presence of psychiatric disorders other than the ones described and, for the "pure" GAD group, the presence of sporadic panic attacks.

The severity of phobic symptoms at the time of the challenge was assessed by the Fear Questionnaire (FQ) (range, 0–120), a self-rating scale composed of 3 subscales scoring agoraphobia (FQ-AGO), social phobia (FQ-SOC), and blood injury phobia (FQ-BI).[43] The severity of panic symptoms was evaluated by the number of spontaneous panic attacks in the last month and by the severity of agoraphobic avoidance according to DSM-IV classification.

At the time of the challenge test, all subjects had to have not taken any psychotropic medications during the previous 2 weeks. They were asked to refrain from alcohol for at least 36 hours, beverages containing xanthine for at least 8 hours, and food or smoking for at least 2 hours preceding the test.

Apparatus

Two different gas mixtures were employed: compressed air (placebo) and a mixture of 35% CO_2 and 65% oxygen (O_2). Both gases were inhaled through the same self-administration mask. Vital capacity was evaluated by a respirometer (Wright respirometer Mark 20, Ferraris Medical Limited, London, U.K.) connected to the self-administration mask. The same respirometer measured the gas volume delivered in each inhalation.

Procedure

All subjects were tested in a double-blind, randomized, crossover design, according to the method described by Griez et al.[29] Subjects were informed that they would be inhaling 2 harmless gas mixtures containing different percentages of CO_2 and O_2 and they might experience some discomfort, ranging from a few neurovegetative symptoms to a definite sensation of anxiety/discomfort with several somatic and/or cognitive sensations, but the term *panic attack* was not mentioned. Vital capacity was measured, and baseline anxiety was assessed via the State-Trait Anxiety Inventory for state anxiety (STAI).[44] Each subject then inhaled 1 vital capacity of 35% CO_2/65% O_2 or of compressed air, in a randomly assigned order, at an interval of 25–30 minutes. At the end of each inhalation, subjects were asked to hold their breath for 4 seconds. The test was considered valid only if the subject had inhaled at least 80% of the previously measured vital capacity.

Immediately before and after each inhalation (air or CO_2), anxiety was evaluated by the Panic Symptom List (PSL-III-R),[45] a self-rating questionnaire assessing the 13 panic symptoms described in DSM-III-R/IV on a 5-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very intense) leading to a total symptom score (TSS) (range, 0–52), and a visual analogue scale for anxiety (VAS-A) describing the degree of global subjective anxiety on a continuum from 0 (no anxiety present) to 100 (the worst anxiety imaginable).

Quantitative Assessment

The anxiety reactivity to 35% CO_2 inhalations was evaluated as the percentage of maximum increment or decrement in score possible on the VAS-A (Δ% VAS-A),[40] calculated as follows:

1. If ΔVAS-A (post-CO_2 VAS-A values minus pre-CO_2 VAS-A values) was positive, then
   Δ% VAS-A = ΔVAS-A × 100/(100 – VAS-A before CO_2).
2. If ΔVAS-A was negative, then
   Δ% VAS-A = ΔVAS-A × 100/VAS-A before CO_2.

The symptomatologic reaction to CO_2 was evaluated as ΔTSS (TSS postinhalation – TSS before inhalation).

Qualitative Assessment

According to the ideal threshold obtained by receiver operating characteristic (ROC) analysis of the 35% CO_2 challenge,[46] the reaction was considered "positive" if Δ% VAS-A ≥ 26 and "negative" if Δ% VAS-A < 26.

Data Analyses

Nonparametric statistics were used for data analyses. To assess the significance of any differences in continuously distributed variables in the 4 groups, the Kruskal-Wallis test and post hoc Mann-Whitney test with Bonferroni correction were applied. Chi-square analyses were applied to compare the proportions of positive reactions and sex distributions in the 4 groups.

Mann-Whitney tests were applied to analyze order-effects of CO_2/air-placebo administration for the whole group of subjects tested and for each group separately.

A logistic regression analysis was applied to evaluate the role of the diagnosis of panic disorder (–1 = absent, 1 = present), the diagnosis of GAD (–1 = absent, 1 = present), baseline VAS-A score (range, –1 to 1, centered around 0), and age (range, –1 to 1, centered around 0) as predictors of the response (–1 = negative, 1 = positive) to CO_2.

The Pearson product moment correlation was applied to evaluate the relationships between STAI scores and VAS-A scores before CO_2 or Δ% VAS-A among patients. Wilcoxon signed rank tests were applied to compare VAS-A scores and TSS before and after both air placebo and CO_2 stimulation.

RESULTS

Clinical and demographic characteristics of the sample are listed in Table 1. The Kruskal-Wallis test showed a significant "Diagnosis" effect for age ($\chi^2 = 10.5$, $p < .02$) and for FQ subscales (FQ-AGO: $\chi^2 = 13.6$, $p < .003$; FQ-BI: $\chi^2 = 21.5$, $p < .002$; FQ-SOC: $\chi^2 = 13.7$, $p < .004$). Post hoc Mann-Whitney test comparisons were performed with Bonferroni correction. GAD patients were significantly older ($z = –3.0$, $p < .02$) than controls. FQ-AGO scores were significantly higher in panic disorder patients ($z = –3.0$, $p < .02$) than in controls. FQ-BI scores were significantly higher (GAD vs. controls: $z = –2.8$, $p < .04$; GAD/panic disorder vs. controls: $z = –3.7$, $p < .01$; panic disorder vs. controls: $z = –3.8$, $p < .01$) in patients' groups than in controls. FQ-SOC scores were significantly higher ($z = –3.3$, $p < .01$) in GAD/panic disorder than in GAD patients. Patterns of distribution for sex in the 4 groups and for agoraphobia between GAD/panic disorder and panic disorder patients did not differ significantly. Ages at onset for panic disorder and for GAD among the GAD/panic disorder patients did not differ significantly from ages at onset among panic disorder and GAD patients. The number of spontaneous panic attacks per week during the month preceding the challenge did not significantly differ between GAD/panic disorder and panic disorder patients.

Baseline anxiety, expressed by STAI scores, and reactivity to 35% CO_2 and air are reported in Table 2. The Kruskal-Wallis test showed a significant "Diagnosis" effect for baseline anxiety expressed as both STAI scores ($\chi^2 = 23.6$, $p < .0001$) and VAS-A scores before CO_2 challenge ($\chi^2 = 24.1$, $p < .0001$). Post hoc Mann-Whitney test comparisons with Bonferroni correction showed significantly greater baseline anxiety in patients with panic disorder (STAI: $z = –3.3$, $p < .01$; VAS-A: $z = –2.9$, $p < .03$),

Table 1. Demographic and Clinical Characteristics of Patient Sample[a]

Variable	Controls (N = 12)	GAD (N = 13)	GAD/Panic Disorder (N = 10)	Panic Disorder (N = 15)
Age, y, mean ± SD	27.5 ± 5.1	39.1 ± 9.4	40.0 ± 12.8	35.8 ± 11.1
Sex, male, N (%)	2 (17%)	3 (23%)	6 (60%)	4 (27%)
Age at onset, y				
Panic attacks				
Mean ± SD	. . .	. . .	30.4 ± 10.9	27.5 ± 11.3
Range	. . .	. . .	18–45	17–58
GAD				
Mean ± SD	. . .	28.3 ± 9.4	32.2 ± 11.8	. . .
Range	. . .	17–49	16–48	. . .
Onset for GAD/ panic disorder patients, N (%)				
GAD before unexpected panic attacks	. . .	. . .	4 (40%)	. . .
Unexpected panic attacks before GAD	. . .	. . .	4 (40%)	. . .
Doubtful	. . .	. . .	3 (30%)	. . .
No. of spontaneous panic attacks/wk in last mo	0	0	1.6 ± 1.4	1.5 ± 2.3
Agoraphobia, N (%)				
None	. . .	. . .	2 (20%)	4 (27%)
Mild	. . .	. . .	4 (40%)	5 (33%)
Moderate	. . .	. . .	3 (30%)	4 (27%)
Severe	. . .	. . .	1 (10%)	2 (13%)
Fear Questionnaire score, mean ± SD				
FQ-AGO	2.1 ± 4.0	3.4 ± 3.6	10.9 ± 8.0	11.8 ± 9.7
FQ-SOC	10.1 ± 6.3	6.1 ± 4.2	21.5 ± 10.0	11.5 ± 9.2
FQ-BI	4.7 ± 3.6	16.0 ± 11.8	23.1 ± 8.7	14.8 ± 5.7

[a]Abbreviations: FQ-AGO = Fear Questionnaire, agoraphobia subscale; FQ-BI = Fear Questionnaire, blood injury phobia subscale; FQ-SOC = Fear Questionnaire, social phobia subscale; GAD = generalized anxiety disorder. Symbol: . . . = not applicable.

Table 2. Baseline Anxiety and Reactivity to 35% CO_2 Inhalations in Patient Groups and Healthy Controls[a]

Variable	Controls (N = 12)	GAD (N = 13)	GAD/Panic Disorder (N = 10)	Panic Disorder (N = 15)
STAI score	30.8 ± 6.0	48.0 ± 12.0	56.3 ± 11.0	43.7 ± 8.6
Air placebo				
VAS-A score before inhalation	7.4 ± 11.4	23.2 ± 17.6	53.2 ± 11.8	31.6 ± 24.4
VAS-A score after inhalation	5.6 ± 9.4	15.6 ± 17.6	57.2 ± 19.1	30.3 ± 16.0
TSS before inhalation	0.5 ± 0.8	3.2 ± 3.2	9.8 ± 3.4	5.4 ± 6.0
TSS after inhalation	0.8 ± 1.1	2.3 ± 3.4	6.3 ± 3.4	4.3 ± 6.6
Δ% VAS-A	–26.8 ± 45.5	–30.2 ± 43.5	9.9 ± 26.4	–7.9 ± 32.0
ΔTSS	0.3 ± 1.1	–0.8 ± 2.2	–3.4 ± 5.7	–1.1 ± 6.0
35% CO_2/65% O_2				
VAS-A score before inhalation	7.7 ± 9.3	21.6 ± 16.6	50.5 ± 17.4	25.5 ± 16.9
VAS-A score after inhalation	23.3 ± 25.4	24.5 ± 15.1	83.6 ± 21.1	68.3 ± 24.4
TSS before inhalation	0.8 ± 1.1	3.4 ± 3.0	9.6 ± 8.1	3.6 ± 4.6
TSS after inhalation	6.3 ± 4.8	8.2 ± 5.8	18.6 ± 6.8	17.4 ± 9.7
Δ% VAS-A	10.2 ± 42.0	–2.8 ± 31.6	68.9 ± 37.2	54.9 ± 38.5
ΔTSS	5.6 ± 5.0	4.8 ± 4.1	9.0 ± 7.0	13.8 ± 9.2
Positive responses, N (%)				
CO_2	3 (25%)	1 (8%)	9 (90%)	12 (80%)
Air	0 (0%)	0 (0%)	3 (30%)	2 (13%)

[a]All values reported as mean ± SD unless otherwise noted. Abbreviations: CO_2 = carbon dioxide, O_2 = oxygen, STAI = State-Trait Anxiety Inventory, TSS = total symptom score on the Panic Symptom List, VAS-A = visual analogue scale for anxiety.

GAD/panic disorder (STAI: $z = -3.8$, $p < .01$; VAS-A: $z = -4.0$, $p < .02$), and GAD (STAI: $z = -3.4$, $p < .01$; VAS-A: $z = -2.7$, $p < .05$) than in controls. GAD/panic disorder patients showed significantly higher (STAI: $z = -3.3$, $p < .01$; VAS-A: $z = -3.0$, $p < .02$) baseline anxiety than panic disorder patients. GAD/panic disorder patients showed significantly higher scores on the VAS-A before CO_2 administration ($z = -3.4$, $p < .01$), but not on the STAI, than GAD patients. There were no significant differences for STAI scores comparing positive with negative reactors. There was a significant correlation between STAI scores and VAS-A scores before CO_2 challenge ($r = .57$, $p < .001$). No correlation was found between STAI scores and Δ% VAS-A in either the whole sample or the patient groups. Mann-Whitney tests showed no significant order effects on Δ% VAS-A and ΔTSS after both air placebo and 35% CO_2 inhalations.

Kruskal-Wallis tests showed a significant "Diagnosis" effect for Δ% VAS-A ($\chi^2 = 21.9$, $p < .001$) and ΔTSS ($\chi^2 = 9.8$, $p < .03$) after the 35% CO_2 challenge. Post hoc Mann-Whitney test comparisons with Bonferroni correction showed similar Δ% VAS-A in panic disorder and GAD/panic disorder patients that was stronger than in GAD patients (vs. GAD/panic disorder: $z = -3.4$, $p < .01$; vs. panic disorder: $z = -3.6$, $p < .02$) and controls (vs. GAD/panic disorder: $z = -2.8$, $p < .03$; vs. panic disorder: $z = -2.9$, $p < .03$), whereas ΔTSS was significantly higher ($z = -2.7$, $p < .05$) in panic disorder than in GAD patients. No significant "Diagnosis" effects were found for Δ% VAS-A and ΔTSS after air placebo inhalations. Wilcoxon signed rank tests comparing pre-post values showed significant increase in VAS-A scores after 35% CO_2 inhalations for panic disorder patients ($z = -3.2$, $p < .002$) and GAD/panic disorder patients ($z = -2.7$, $p < .007$), whereas no significant modifications were found for GAD patients and controls. Significant increases in TSS occurred after CO_2 inhalations for all groups (GAD: $z = -2.8$, $p < .005$; GAD/panic disorder: $z = -2.3$, $p < .03$; panic disorder: $z = -3.3$, $p < .002$; controls: $z = -2.9$, $p < .004$). No significant modifications of either VAS-A scores or TSS after air inhalations were found. Logistic regression analysis showed that only the presence of panic disorder was a significant (estimate parameter, 1.37 ± 0.46; $t = 2.98$, $p < .005$) predictor of CO_2 reactivity, while the presence of GAD (estimate parameter, –0.42 ± 0.52), baseline VAS-A score (estimate parameter, –0.92 ± 0.97), and age

(estimate parameter, –0.07 ± 0.72) were not significant predictors. Maximum likelihood estimation showed a significant fit of the estimated model to the data ($\chi^2 = 26.4$, df = 4, $p < .0001$), with a proportion of explained variance of 0.47 (R = 0.69).

Finally, there were different patterns of distribution ($\chi^2 = 24.1$, df = 3, $p < .0001$) for rates of positive responses to 35% CO_2 inhalation in the 4 groups. Post hoc 2 × 2 chi-square analyses showed similar rates of positive responses in panic disorder and in GAD/panic disorder patients, significantly higher than in GAD patients and in controls. No significant differences were found when comparing rates of positive responders to air placebo.

DISCUSSION

The results of this study indicate that GAD per se is not characterized by an abnormal sensitivity to CO_2. With regard to the subjective anxiety reaction to the 35% CO_2 challenge, as assessed both by quantitative (Δ% VAS-A) and by qualitative evaluation (rate of positive responses), GAD patients reported a reaction similar to that of healthy controls and significantly lower than that reported by panic disorder patients. Unlike for panic disorder patients, no significant modifications of subjective anxiety after CO_2 stimulation were detected for either GAD patients or healthy controls. Patients with comorbid GAD and panic disorder reported a subjective anxiety reaction and a rate of positive reactors to CO_2 that were comparable to those reported by panic disorder patients and significantly higher than those reported by GAD patients without panic disorder.

Consideration of the panic symptomatology reaction revealed that although CO_2 stimulation induced a significant increase in panic symptomatology in all 4 groups, the reaction of GAD patients was lower than that observed in panic disorder patients and similar to that of healthy controls. Panic symptomatologic reaction to CO_2 was not significantly different in patients with comorbid GAD and panic disorder than in patients with panic disorder alone.

Our findings partially confirm the results reported by Verburg et al.,[39] who reported a lower subjective anxiety reactivity to CO_2 in GAD than in panic disorder patients but a similar high increase in "autonomic panic symptoms." In our study, GAD patients showed a lower reactivity on both subjective anxiety and panic symptomatology. We are not able to explain the reasons of this difference, since the procedure used was very similar. It should be noted, however, that different sampling procedures were used. GAD patients from the study by Verburg et al.[39] were recruited from a nonclinical population, whereas our patients were from a clinical population.

The difference in reactivity between panic disorder patients and GAD patients cannot be attributed to differences in baseline anxiety, since there were no significant differences in scores for either the VAS-A before CO_2 challenge or the STAI scale. In addition, although baseline anxiety was lower in controls than in GAD patients, neither group reacted significantly to 35% CO_2 inhalation. Finally, there was no significant correlation between CO_2 reactivity and either STAI or VAS-A scores before CO_2.

Although patients with GAD and those with panic disorder share a high level of anxiety, and although some investigators question the separation of these 2 anxiety disorders, our study indicates that the 35% CO_2 hypersensitivity is a specific marker for panic disorder and emphasizes the distinction between these 2 disorders. The lack of any significant influence of comorbidity for GAD on the anxiety hyperreactivity of panic disorder patients to 35% CO_2 inhalation argues against an overlap of the pathogenetic mechanisms for these 2 major anxiety disorders.

These results support the idea that the simple presence of an anxiety disorder is not sufficient to explain CO_2 reactivity and suggest that CO_2 reactivity might be a useful marker for panic disorder. An evaluation of data from the literature seems to support the existence of 2 separate subgroups of anxiety disorders. Patients with social phobia[31,33,34] and those with situational simple phobia[38] seem to react to 35% CO_2 more strongly than do controls, and it could be speculated that an abnormal vulnerability to CO_2 might identify a panic-phobic spectrum whose main clinical characteristics are represented by panic attacks, anticipatory anxiety, and the development of avoidance behaviors. On the other hand, patients with OCD and GAD are not hypersensitive to 35% CO_2 and thus are different in this aspect from the panic-phobic spectrum patients. These observations are also consistent with the idea that panic and anxiety/fear are separate psychophysiologic entities,[47,48] the first possibly related to a specific adaptive mechanism focused on suffocation and thus involving respiratory control mechanisms, the second related to a more general adaptive system involving the activation of stress mechanisms by nonspecific threatening stimuli.

In conclusion, although based on a limited sample of GAD patients, this study (1) supports the DSM-IV distinction between panic disorder and GAD, suggesting that at least some of their pathogenetic mechanisms are different, and (2) confirms the idea that the 35% CO_2 challenge might be a valid tool for the investigation of differences between anxiety disorders.

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