

Specificity of Panic Response to CO₂ Inhalation in Panic Disorder: A Comparison With Major Depression and Premenstrual Dysphoric Disorder

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Objective: The behavioral response to CO₂ inhalation has been used to differentiate panic disorder patients from normal subjects and other clinical populations. This study extended examination of the diagnostic specificity of CO₂-induced anxiety by testing panic disorder patients and clinical populations with reported low and high sensitivity to CO₂ inhalation (patients with major depression and patients with premenstrual dysphoric disorder, respectively).

Method: The behavioral responses to inhalation of 5% and 7% CO₂, administered by means of a respiratory canopy, were studied in 50 patients with panic disorder, 21 with major depression, and 10 with premenstrual dysphoric disorder and in 34 normal comparison subjects. Occurrence of panic attacks was judged with DSM-IV criteria by a blind rater. Subjects were rated on three behavioral scales at baseline and after each CO₂ inhalation.

Results: Panic disorder patients had a higher rate of CO₂-induced panic attacks than depressed patients and normal subjects, whose panic rates were not distinguishable. The panic rate for patients with premenstrual dysphoric disorder was similar to that for panic disorder patients and higher than that for normal subjects. Subjects with CO₂-induced panic attacks had similarly high ratings on the behavioral scales, regardless of diagnosis, including the small number of panicking normal subjects. Seven percent CO₂ was a more robust panicogen than 5%, and response to 7% CO₂ better distinguished panic disorder patients from normal subjects than response to 5% CO₂.

Conclusions: Patients with panic disorder and patients with premenstrual dysphoric disorder are highly susceptible to CO₂-induced panic attacks, and depressed patients appear to be insensitive to CO₂ inhalation. The symptoms of CO₂-induced panic attacks have a similar intensity regardless of the subject's diagnosis.

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Modern psychiatric nosology has put a premium on careful delineation of discrete categories of illness. This is particularly true for the anxiety disorders. Beginning with DSM-III in 1980, broad categories such as anxiety neurosis have been replaced by more specific categories such as panic disorder, social phobia, and generalized anxiety disorder. Moreover, the anxiety disorders are held to be distinct from depression.

One strategy for differentiating these disorders is to observe differences in response to stimuli that elicit common symptoms of each disorder. Carbon dioxide (CO₂) inhalation is one such stimulus that has been shown to produce a greater response in panic disorder subjects than in normal comparison subjects in many studies (1–5). The question of whether CO₂ inhalation effects are specific to panic disorder or also occur among subjects with other psychiatric disorders has recently been tested in several studies. Most other diagnostic groups have not shown the high rates of anxiety and panic attacks evoked in panic disorder.

Among the anxiety disorders, social phobia appears to be associated with panic rates intermediate between those for normal comparison subjects and for panic disorder patients when studied with the respiratory canopy method (6), and panic rates similar to those for panic disorder patients when studied with the single-breath 35% CO₂ method (7, 8). However, panic rates in response to CO₂ among patients with generalized anxiety disorder and patients with obsessive-compulsive disorder (9–11) have not been distinguishable from those among normal comparison subjects.

With regard to the mood disorders, two early studies found that patients with depressive-spectrum illnesses demonstrated less ventilatory responsiveness to CO₂, compared with normal subjects (12, 13). More recently, the CO₂ behavioral response of subjects with major depression was studied, and no differences in panic rates between depressed and normal comparison subjects were found (14). Women with premenstrual dysphoric disorder, which is categorized as a mood disorder not otherwise specified in DSM-IV, have demonstrated markedly high

rates of panic in response to CO₂ challenge, similar to rates for panic disorder patients (15). Patients with premenstrual dysphoric disorder have also been shown to be sensitive to lactate-induced panic attacks (16, 17).

This study had three major aims. The first was to further determine the specificity of CO₂-induced anxiety by testing two diagnostic groups (depressed patients and patients with premenstrual dysphoric disorder). We hypothesized that 1) the panic rates of panic disorder subjects in response to CO₂ inhalation will be greater than those of normal comparison subjects and depressed patients, but indiscriminable from those of subjects with premenstrual dysphoric disorder, 2) the panic rates of subjects with premenstrual dysphoric disorder will be greater than those of normal comparison subjects and depressed patients, and 3) the panic rates of normal comparison subjects and depressed patients will not differ significantly from each other.

Despite the relative specificity of CO₂-evoked panic attacks to panic disorder, panic attacks can be induced, albeit at low rates, across all diagnostic groups. Thus, a second aim of this study was to establish whether CO₂-induced panic attacks in subjects with panic disorder differ in behavioral response (symptom intensity) from those in subjects without panic disorder. Our hypothesis was that the quantitative panic response would be more similar than different across diagnostic groups.

The third aim was to confirm our earlier work demonstrating a more robust separation in panic rates between panic disorder and comparison groups in response to inhalation of 7% versus 5% CO₂.

The present data come from a larger study that used CO₂ inhalation to examine the ventilatory physiology of panic disorder patients. Data on the behavioral response to CO₂ inhalation are presented here. Other aspects of this study, including the physiological assessment of CO₂ sensitivity, the effect of instructional sets, and the effects of pharmacologic and psychologic treatment on CO₂ sensitivity, are reported elsewhere (18).

Method

Subjects

After subjects received a clinical diagnosis of panic disorder, major depression, or premenstrual dysphoric disorder made by a study psychiatrist, they were interviewed by a second clinician with the Structured Clinical Interview for DSM-IV (SCID) (19). If the two clinicians disagreed on the diagnosis, they met to confer. If a consensus on the diagnosis could not be reached, the subject was not enrolled. Potential panic disorder subjects were excluded if they currently or within the last 6 months had a diagnosis of a major depressive episode, eating disorder, or substance abuse/dependence, or if they had any lifetime history of obsessive compulsive disorder, schizophrenia, or bipolar affective disorder. The presence of another anxiety disorder or dysthymia was allowed if the disorder was considered secondary in clinical importance to panic disorder by both the patient and evaluating clinician. Potential subjects with major depression were screened and evalu-

ated in the same manner as panic disorder subjects. Exclusion criteria were no current (or within the last 6 months) diagnosis of substance abuse/dependence or eating disorder and no lifetime history of schizophrenia, bipolar affective disorder, or any anxiety disorder (with the exception of a specific phobia). Potential subjects with premenstrual dysphoric disorder were screened and evaluated in the same manner. A preliminary diagnosis of premenstrual dysphoric disorder was made by the evaluating psychiatrist, and all other axis I disorders were ruled out on the basis of an interview with the SCID. Subjects were then asked to complete prospective daily rating scales over a period of 2 months to describe the frequency and severity of their mood, anxiety, and physical symptoms. The ratings were used to confirm the subject's diagnosis.

Comparison subjects underwent psychiatric interviews with staff psychiatrists and structured clinical interviews with either the Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders (20) or the SCID. Comparison subjects had to be free of any lifetime history of anxiety disorders, major affective disorders, schizophrenia, eating disorders, and current (within the last 6 months) substance abuse/dependence.

All subjects had complete medical evaluations including ECGs, blood chemistries, and urine drug screens. Subjects were required to be free of all psychoactive drugs for 2 weeks before testing. Panic disorder subjects were permitted the use of a benzodiazepine, up to the equivalent of 10 mg of diazepam per day, until 72 hours before testing; however, only one subject used a benzodiazepine within the 2 weeks before the study. Informed consent was obtained from all subjects, who were told that breathing CO₂, while not harmful, might cause anxiety or panic attacks. Subjects were unaware of the order or length of presentation of room air, 5% CO₂, and 7% CO₂ (single-blind design). The study was approved by the institutional review board of the New York State Psychiatric Institute.

Study Procedures

The subject was placed in the supine position with his or her head enclosed in a clear plastic respiratory canopy (1). The canopy was completely sealed but allowed the subject to see and hear at all times. Subjects were instructed how to open the canopy should they feel the need to exit quickly. Breath-by-breath spirometry and other physiologic data were recorded throughout the period the subject was in the respiratory canopy. The study consisted of five 20-minute respiratory periods: 1) room air breathing (baseline), 2) 5% CO₂ inhalation, 3) room air breathing (recovery baseline), 4) 7% CO₂ inhalation, 5) room air breathing (second recovery baseline). Panic attack assessments and behavioral rating scales were administered when the subject entered the respiratory canopy and at the end of each respiratory period. A blinded rater was present in the room with the subject throughout the study. Raters were trained to reliably make the judgment of whether a panic attack occurred. Raters regarded an attack as an acute event in which the subjects exhibited four or more physical symptoms of panic according to the DSM-IV criteria in addition to a crescendo-like increase in anxiety and fear. Raters were not permitted to ask the subjects if they had or had not experienced a panic attack, as we felt this would compromise the blind. The rating scales included the Acute Panic Inventory (21), the Borg scale of perceived exertion (a 10-point measure of respiratory effort or breathlessness) (22), and a 10-point anxiety scale, on which 1 represented no anxiety and 10 represented the highest level of anxiety experienced. If a subject wished to stop any respiratory period before 20 minutes elapsed, the behavioral rating scales were administered and a determination of whether a panic attack occurred was made.

TABLE 1. Demographic and Clinical Characteristics of Subjects With Three Psychiatric Diagnoses and Normal Comparison Subjects in a Study of Diagnostic Specificity of Panic Response to CO₂ Inhalation

Characteristic	Patients With Panic Disorder (N=50)		Patients With Major Depression (N=21)		Patients With Premenstrual Dysphoric Disorder (N=10)		Normal Comparison Subjects (N=34)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	32.22	7.7	34.33	8.4	32.30	6.6	29.97	8.1
Sex	N	%	N	%	N	%	N	%
Men	28	56.0	11	52.4	0	0.0	19	55.9
Women	22	44.0	10	47.6	10	100.0	15	44.1
Secondary diagnosis								
Generalized anxiety disorder	2	4.0	0	0.0	0	0.0		
Social phobia	6	12.0	0	0.0	0	0.0		
Specific phobia	4	8.0	1	4.8	0	0.0		
Dysthymia	4	8.0	3	14.3	1	10.0		
Past history of substance abuse	5	10.0	1	4.8	0	0.0		

Data Analysis

Comparison of panic rates. To test our main hypotheses regarding panic rates in the four diagnostic groups (panic disorder, major depression, premenstrual dysphoric disorder, normal comparison), an overall comparison of the rates of panic in response to 5% CO₂ and 7% CO₂ inhalation across the four groups was made with a chi-square test. Post hoc analyses were performed by using pair-wise chi-square tests with Yates's correction or, where appropriate, Fisher's exact tests, with values corrected for multiple comparisons (Bonferroni correction).

Comparison of response to CO₂ inhalation. To determine whether the behavioral response to CO₂ inhalation was a function of group membership, of having a panic attack, or of both factors, we used a four-by-two-by-two repeated measures analysis of variance (ANOVA) (four groups [panic disorder patients, depressed patients, patients with premenstrual dysphoric disorder, and normal comparison subjects] by two categories of judgment about panic status in response to CO₂ inhalation [yes or no] by two time points [end of the baseline period immediately before the intervention and end of the CO₂ intervention]). The ANOVA was chosen, rather than an analysis of covariance, because baseline differences were assumed in a study of nonrandom groups. Thus, an ANOVA was performed for each of the three rating scales (Acute Panic Inventory, 10-point anxiety scale, Borg breathlessness scale), with the four diagnostic groups as one factor, panic status as a second factor, and the scale score as the dependent variable. In these analyses, significant diagnostic group-by-time interactions would indicate a differential behavioral response to CO₂ inhalation on the basis of diagnosis; significant interactions of panic status (yes or no) and time would indicate differential behavioral response on the basis of whether a panic attack occurred; and a significant three-way interaction would indicate differential behavioral response on the basis of both diagnosis and whether a panic attack occurred. The analyses were done separately for 5% and 7% CO₂ inhalation. Significant interactions were followed by post hoc testing with Tukey's honestly significant difference test for unequal Ns (Spjotvoll/Stoline test).

To compare the effects of 5% versus 7% CO₂ within each group, separate exact binomial (McNemar) tests for each group were performed on the differences in panic rates between the two conditions.

All p values reported are two-tailed; the significance level was set at 0.05.

Results

There were no disagreements on the primary diagnosis between the interviewing psychiatrist and the SCID clinician. Rare disagreements on secondary diagnoses were all resolved in conference. A total of 124 subjects entered the study. Of these subjects, two panic disorder subjects were removed from the study due to incomplete data, and seven subjects with premenstrual dysphoric disorder were excluded for failure to complete enough prospective rating scales to confirm the diagnosis. The 115 remaining subjects consisted of 1) 50 patients who met the DSM-IV criteria for panic disorder with or without agoraphobia (78.0% and 22.0%, respectively); 2) 21 patients who met the DSM-IV criteria for major depression, single episode or recurrent; 3) 10 patients who met the DSM-IV (appendix B) criteria for premenstrual dysphoric disorder; and 4) 34 normal comparison subjects, with no psychiatric diagnosis. Table 1 presents demographic and clinical data for the groups. There were no significant age differences among the groups.

An attempt was made to study each subject with premenstrual dysphoric disorder twice, once during the follicular phase and once during the luteal phase. However, due to concerns about treatment delays, only five of the 10 subjects with premenstrual dysphoric disorder completed both studies. The data reported here are from the first respiratory procedure performed for each of the 10 subjects with premenstrual dysphoric disorder (four in the luteal phase and six in the follicular phase). Due to the small number of subjects with premenstrual dysphoric disorder, a lack of sufficient power precluded meaningful analysis of the effect of menstrual phase.

Baseline Ratings

Rating scales were administered immediately upon the subjects' entering the respiratory canopy and again at the end of the baseline room air period, after subjects had been in the canopy breathing room air for 20 minutes. Independent two-way repeated measures ANOVA was used

TABLE 2. Intensity of Panic Symptoms Before CO₂ Inhalation Among Subjects With Three Psychiatric Diagnoses and Normal Comparison Subjects and Significant Post Hoc Group Differences

Measure and Post Hoc Analysis	Patients With Panic Disorder (N=50)		Patients With Major Depression (N=21)		Patients With Premenstrual Dysphoric Disorder (N=10)		Normal Comparison Subjects (N=34)		ANOVA			Significant Post Hoc Analyses ^a
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p	
Score on Acute Panic Inventory (21)	10.20	9.42	4.14	3.47	3.80	4.87	0.47	1.13	15.50	3, 111	0.001	p<0.02 p<0.001
Panic disorder versus major depression												
Panic disorder versus normal comparison												
Score on 10-point anxiety scale	3.12	2.11	1.95	1.32	2.30	1.77	1.15	0.36	10.54	3, 111	0.001	p<0.001
Panic disorder versus normal comparison												
Score on Borg scale of perceived exertion (breathlessness) (22)	0.90	1.23	0.38	0.60	0.40	1.27	0.06	0.24	5.68	3, 111	0.001	p=0.002
Panic disorder versus normal comparison												

^a Tukey's honestly significant difference test for unequal Ns (Spjotvoll/Stoline test)

TABLE 3. Patients With Three Psychiatric Diagnoses and Normal Comparison Subjects Who Panicked in Response to Inhalation of 5% CO₂ and 7% CO₂

Subject Group and Post Hoc Group Comparison	Patients Responding to Inhalation of 5% CO ₂						Patients Responding to Inhalation of 7% CO ₂					
	Patients Who Panicked			Analysis ^a			Patients Who Panicked			Analysis ^a		
	N	N	%	χ^2	df	p	N	N	%	χ^2	df	p
Subject groups				22.04	3	<0.001 ^b				21.48	3	<0.001 ^b
Patients with panic disorder	50	26	52.0				48	32	66.7			
Patients with premenstrual dysphoric disorder	10	5	50.0				9	5	55.6			
Patients with major depression	21	3	14.3				20	7	35.0			
Normal comparison subjects	34	3	8.8				32	5	15.6			
Post hoc group comparisons												
Panic disorder versus major depression				7.22	1	<0.007 ^b				4.57	1	<0.04
Panic disorder versus premenstrual dysphoric disorder						<1.0 ^c						<0.71 ^c
Panic disorder versus normal comparison				14.86	1	<0.001 ^b				18.12	1	<0.001 ^b
Major depression versus premenstrual dysphoric disorder						<0.08 ^c						<0.42 ^c
Major depression versus normal comparison				0.035	1	<0.86				1.63	1	<0.21
Premenstrual dysphoric disorder versus normal comparison						<0.01 ^c						<0.03 ^c

^a Chi-square test with Yates's correction or Fisher's exact test used for post hoc group comparisons.

^b Significant at the 0.05 level with Bonferroni correction.

^c Fisher's exact test.

to analyze data from each of the three scales (Acute Panic Inventory, the 10-point anxiety scale, and the Borg breathlessness scale,) with the four diagnostic groups (panic disorder, major depression, premenstrual dysphoric disorder, and normal comparison) as the between-subjects factor and time (entry into the canopy and post-20 minutes of room air breathing) as the within-subjects factor. Results revealed significant group effects for all three scales (Acute Panic Inventory: $F=15.81$, $df=3$, 111, $p<0.001$; 10-point anxiety scale: $F=12.24$, $df=3$, 111, $p<0.001$; Borg: $F=7.10$, $df=3$, 111, $p<0.001$). Post hoc testing demonstrated the panic disorder group was the only group consistently distinguished from the normal comparison group, with significantly higher scores on all three scales ($p<0.001$). Panic disorder patients also reported significantly higher scores than major depression patients on the Acute Panic Inventory ($p<0.03$) and on the 10-point anxiety scale ($p<0.04$).

ANOVAs performed on the scale scores obtained at the end of the baseline period revealed significant differences

for all three scales. These results, along with the post hoc analyses, are reported in Table 2. For the analyses of the effects of 5% CO₂ reported in the next section, the scale scores obtained at the end of the 20-minute room air acclimatization period were used as the baseline scores.

Effects of 5% CO₂

CO₂ tolerance. Disregarding panic status, panic disorder subjects terminated 5% CO₂ breathing after a mean of 16.0 minutes (SD=6.5), depressed subjects after 17.6 minutes (SD=4.7), and subjects with premenstrual dysphoric disorder after 15.1 minutes (SD=7.8), while all normal comparison subjects completed the full 20 minutes of the 5% CO₂ inhalation period. An ANOVA performed on this data revealed a significant group effect ($F=3.94$, $df=3$, 111, $p<0.01$). Post hoc testing showed that panic disorder subjects tolerated significantly less 5% CO₂ than comparison subjects ($p<0.03$).

Panic rates. Fifty panic disorder subjects, 21 depressed subjects, 10 subjects with premenstrual dysphoric disorder,

TABLE 4. Change in Intensity of Panic Symptoms From Baseline to End of a 20-Minute Period of Inhalation of 5% CO₂ Among Subjects With Three Psychiatric Diagnoses and Normal Comparison Subjects Who Did and Did Not Panic in Response to the CO₂ Inhalation

Subject Group and Significant Group Comparison	Change in Score on Acute Panic Inventory					Change in Score on 10-Point Anxiety Scale					Change in Score on Borg Scale of Perceived Exertion (Breathlessness)				
	Mean	SD	F	df	p	Mean	SD	F	df	p	Mean	SD	F	df	p
Subject groups															
Panic disorder															
Panickers (N=26)	19.65	10.26				3.42	2.23				4.58	2.63			
Nonpanickers (N=24)	6.75	5.18				0.87	1.36				2.79	2.02			
Major depression															
Panickers (N=3)	15.33	7.77				4.67	1.53				6.67	0.58			
Nonpanickers (N=18)	7.66	5.76				0.83	0.79				2.89	1.68			
Premenstrual dysphoric disorder															
Panickers (N=5)	14.20	6.14				3.80	1.64				4.60	1.82			
Nonpanickers (N=5)	8.80	7.26				1.60	2.07				3.20	1.79			
Normal comparison subjects															
Panickers (N=3)	22.33	12.10				6.00	1.73				9.00	1.73			
Nonpanickers (N=31)	4.10	4.04				0.71	0.94				2.61	1.71			
Significant group comparisons															
Interaction of diagnostic group and panic status			4.69	3, 107	0.004 ^a										
Interaction of panic status and time ^b			33.35	1, 107	0.001 ^a										
Interaction of diagnostic group, panic status, and time ^b						2.98	3, 107	<0.04 ^a			4.49	3, 107	0.005 ^a		

^a Significant at the <0.05 level (two-tailed test).^b End of the baseline period immediately before CO₂ inhalation versus end of the period of CO₂ inhalation.

der, and 34 normal comparison subjects underwent the 5% CO₂ inhalation procedure. Rates of panic in response to 5% CO₂ inhalation are reported in Table 3. Chi square analysis revealed a significant difference in panic rates across groups ($\chi^2=22.04$, $df=3$, $p<0.001$). Follow-up 2×2 comparisons (Table 3) revealed significant differences in panic rates in response to 5% CO₂ between panic disorder subjects and both depressed and normal comparison subjects but not subjects with premenstrual dysphoric disorder. Panic rates for the depressed subjects did not differ from those for the subjects with premenstrual dysphoric disorder or for the normal comparison subjects.

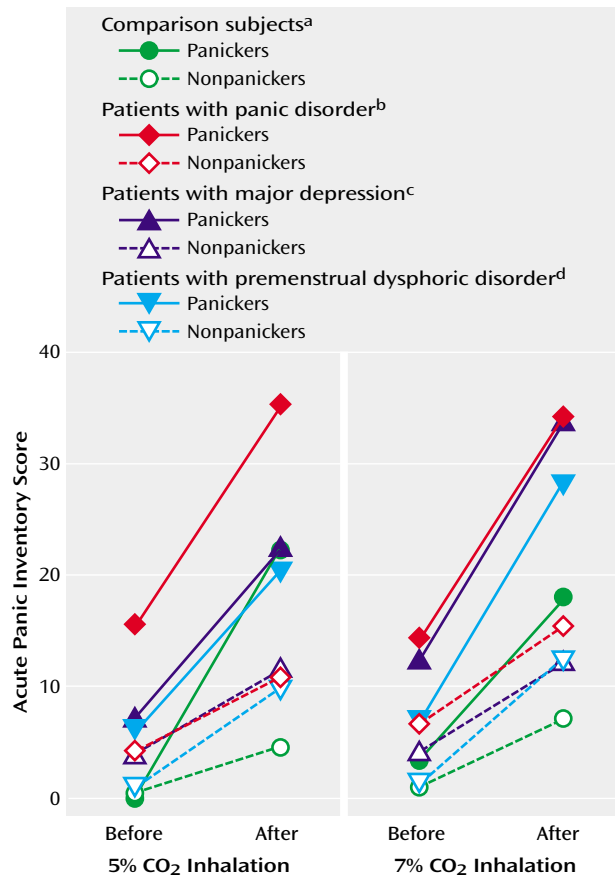
Rating scales. Table 4 shows the change in rating scale data for 5% CO₂ inhalation, broken down by whether subjects panicked. To aid interpretation, results are presented graphically in Figure 1, Figure 2, and Figure 3. Repeated measures ANOVAs were performed for each of the three scales by using a $4 \times 2 \times 2$ design (four diagnostic groups, two panic statuses [yes or no], and two time points [end of the resting baseline period immediately before the intervention and end of the CO₂ intervention]).

For the Acute Panic Inventory scores, two significant interactions were revealed: 1) panic status and time and 2) diagnostic group and panic status. The interaction of panic status and time demonstrated that the increase in Acute Panic Inventory scores for panickers in response to 5% CO₂ inhalation was significantly greater than the increase for nonpanickers. However, within panicking subjects, the increase in Acute Panic Inventory scores did not differ significantly across groups; similarly, within non-

panicking subjects, the increase did not differ significantly across groups. Post hoc analyses revealed that subjects who panicked in response to 5% CO₂ had higher Acute Panic Inventory scores before CO₂ inhalation than those who did not panic ($p<0.001$) and that scores after inhalation were higher for panicking subjects than for nonpanicking subjects ($p<0.001$). The interaction of diagnostic group and panic status revealed that the difference in mean pre- and postinhalation Acute Panic Inventory scores between the panicking and nonpanicking subjects was different among diagnostic groups. Post hoc analyses showed that panic disorder subjects who panicked in response to 5% CO₂ inhalation had significantly higher mean Acute Panic Inventory scores than panic disorder subjects who did not panic ($p<0.001$), reflecting their higher baseline scores on that measure. Post hoc testing also revealed that panic disorder subjects who panicked had higher mean Acute Panic Inventory scores than depressed subjects who panicked ($p<0.03$) and nearly significantly higher scores than the normal comparison subjects ($p<0.07$). Thus, the significant interaction of diagnostic group and panic status is attributable to the high baseline Acute Panic Inventory scores of the panic disorder subjects who panicked in response to 5% CO₂ inhalation. Lack of a three-way interaction confirms that the degree of increase in the Acute Panic Inventory scores in response to 5% CO₂ inhalation is a function of panic status rather than diagnostic group membership.

The repeated measures ANOVA performed on the scores on the 10-point anxiety scale revealed a significant three-

FIGURE 1. Mean Scores on the Acute Panic Inventory Before and After Inhalation of 5% CO₂ and 7% CO₂ of Subjects With Three Psychiatric Diagnoses and Normal Comparison Subjects Who Did and Did Not Panic in Response to the CO₂ Inhalation



^a For 5% CO₂ inhalation, N=3 panickers and N=31 nonpanickers; for 7% CO₂ inhalation, N=5 panickers and N=27 nonpanickers.

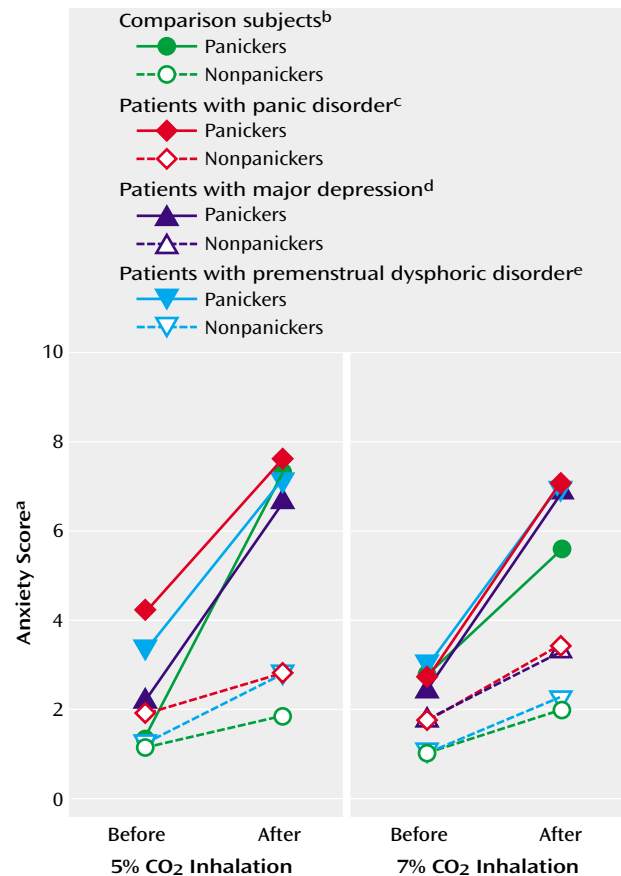
^b For 5% CO₂ inhalation, N=26 panickers and N=24 nonpanickers; for 7% CO₂ inhalation, N=32 panickers and N=16 nonpanickers.

^c For 5% CO₂ inhalation, N=3 panickers and N=18 nonpanickers; for 7% CO₂ inhalation, N=7 panickers and N=13 nonpanickers.

^d For 5% CO₂ inhalation, N=5 panickers and N=5 nonpanickers; for 7% CO₂ inhalation, N=5 panickers and N=4 nonpanickers.

way interaction of diagnostic group, panic status, and time. Results demonstrated the effect of time on anxiety scores to be greater among panickers than nonpanickers. The three-way interaction shows the effect of time to be different for panickers between the four groups, while there is no significant difference in the effect of time across groups for nonpanickers. Post hoc testing confirmed that all subjects who panicked, regardless of diagnostic group and despite baseline differences in anxiety, reported similar end levels of anxiety in response to 5% CO₂ inhalation. The small number of panicking comparison subjects, who had low baseline levels of anxiety, therefore exhibited the greatest increase. The normal comparison group accounted for the three-way interaction, as demonstrated by a lack of a three-way interaction when the analysis was performed without the comparison group.

FIGURE 2. Mean Anxiety Scores Before and After Inhalation of 5% CO₂ and 7% CO₂ of Subjects With Three Psychiatric Diagnoses and Normal Comparison Subjects Who Did and Did Not Panic in Response to the CO₂ Inhalation



^a Measured on a 10-point anxiety scale, on which 1 represents no anxiety and 10 represents the highest possible level of anxiety.

^b For 5% CO₂ inhalation, N=3 panickers and N=31 nonpanickers; for 7% CO₂ inhalation, N=5 panickers and N=27 nonpanickers.

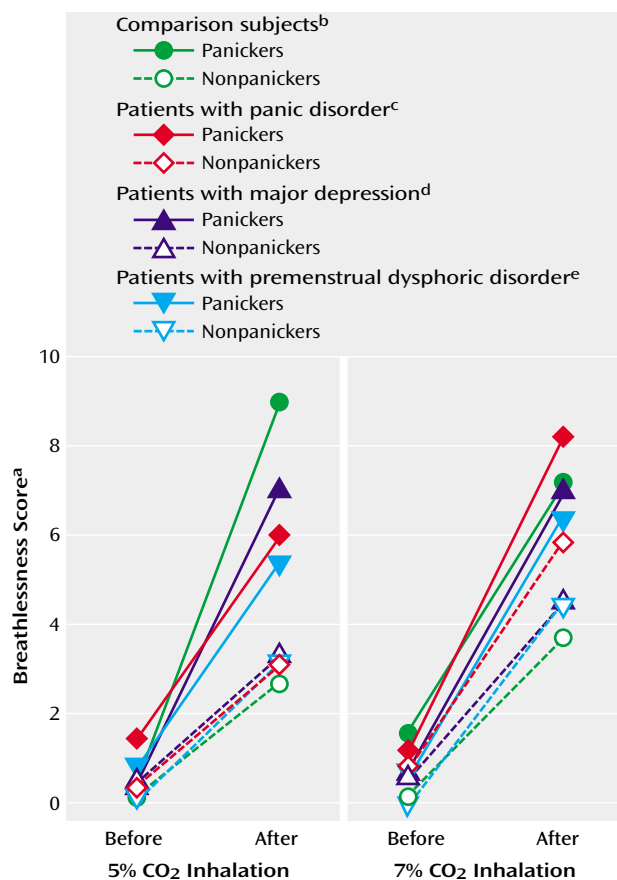
^c For 5% CO₂ inhalation, N=26 panickers and N=24 nonpanickers; for 7% CO₂ inhalation, N=32 panickers and N=16 nonpanickers.

^d For 5% CO₂ inhalation, N=3 panickers and N=18 nonpanickers; for 7% CO₂ inhalation, N=7 panickers and N=13 nonpanickers.

^e For 5% CO₂ inhalation, N=5 panickers and N=5 nonpanickers; for 7% CO₂ inhalation, N=5 panickers and N=4 nonpanickers.

For the Borg breathlessness scale, the repeated measures ANOVA revealed a three-way interaction of diagnostic group, panic status, and time. The effect of time on breathlessness scores was greater among panickers than nonpanickers. The three-way interaction demonstrates the effect of time to be different for panickers across the four groups but not for nonpanickers across the groups. Similar to the finding for the 10-point anxiety scale, the small number of panicking comparison subjects demonstrated the greatest increase in scores on the Borg scale, and when the comparison group was excluded from the analysis, the three-way interaction was lost. Post hoc testing confirmed that there were no preinhalation differences across subjects on the basis of panic status, and no postinhalation differences in scores for panicking sub-

FIGURE 3. Mean Breathlessness Scores Before and After Inhalation of 5% CO₂ and 7% CO₂ of Subjects With Three Psychiatric Diagnoses and Normal Comparison Subjects Who Did and Did Not Panic in Response to the CO₂ Inhalation



^a Measured with the Borg scale of perceived exertion (22).

^b For 5% CO₂ inhalation, N=3 panickers and N=31 nonpanickers; for 7% CO₂ inhalation, N=5 panickers and N=27 nonpanickers.

^c For 5% CO₂ inhalation, N=26 panickers and N=24 nonpanickers; for 7% CO₂ inhalation, N=32 panickers and N=16 nonpanickers.

^d For 5% CO₂ inhalation, N=3 panickers and N=18 nonpanickers; for 7% CO₂ inhalation, N=7 panickers and N=13 nonpanickers.

^e For 5% CO₂ inhalation, N=5 panickers and N=5 nonpanickers; for 7% CO₂ inhalation, N=5 panickers and N=4 nonpanickers.

jects. Panicking comparison subjects, however, demonstrated significantly greater postinhalation breathlessness scores than the nonpanicking subjects in all four groups, while panicking panic disorder subjects were distinguished from nonpanicking subjects in only the comparison, panic disorder, and major depression groups. The postinhalation scores of panicking subjects in the major depression group and the premenstrual dysphoric disorder group were indistinguishable from the postinhalation scores of the three nonpanicking patient groups.

Effects of 7% CO₂

CO₂ tolerance. Forty-eight panic disorder subjects, 20 depressed subjects, nine subjects with premenstrual dysphoric disorder, and 32 normal comparison subjects remained in the respiratory canopy and underwent 7% CO₂

inhalation. Of these 109 subjects, those with panic disorder and premenstrual dysphoric disorder again tolerated the least amount of CO₂ exposure (mean=12.6 minutes, SD=14.4, for panic disorder subjects; mean=14.1 minutes, SD=7.4, for depressed subjects; mean=10.0 minutes, SD=8.2, for subjects with premenstrual dysphoric disorder; and mean=17.4 minutes, SD=5.5, for normal subjects). However, this difference was not significant by ANOVA.

Panic rates. Rates of panic in response to 7% CO₂ are reported in Table 3. Chi-square analysis revealed a significant difference in panic rates across groups ($\chi^2=21.48$, df=3, $p<0.001$). Follow-up 2 \times 2 comparisons of the panic rates in response to 7% CO₂, made with the conservative Bonferroni correction, revealed a significant difference between panic disorder subjects and normal comparison subjects but not subjects with premenstrual dysphoric disorder or depression (Table 3). Panic rates did not differ significantly between the depressed, premenstrual dysphoric disorder, or normal comparison groups. Thus, while 7% CO₂ was more robust in differentiating panic disorder subjects from normal comparison subjects, an increased panic rate in depressed subjects resulted in a loss of the distinction between the panic disorder and depressed groups in response to 7% CO₂, compared with response to 5% CO₂.

Rating scales. Table 5 shows the changes in rating scale scores for the 7% CO₂ period, broken down by whether subjects panicked. To aid interpretation, results are presented graphically in Figure 1, Figure 2, and Figure 3. As in the analyses of data for the 5% CO₂ period, repeated measures ANOVAs were performed for the 7% CO₂ period for each of the three scales.

Results of the repeated measures ANOVA performed on the Acute Panic Inventory scores revealed a significant main effect of group and a significant interaction of panic status and time. Post hoc testing of the group effect showed that the panic disorder subjects had significantly higher scores than the comparison subjects ($p<0.001$) and that the depressed subjects had significantly higher scores than the comparison subjects ($p<0.01$). The interaction of panic status and time revealed that panicking subjects demonstrated greater increases in their scores on the Acute Panic Inventory pre- to postinhalation, compared with nonpanicking subjects. Post hoc testing demonstrated that subjects who panicked in response to 7% CO₂ inhalation had higher Acute Panic Inventory scores preinhalation than those who did not panic ($p<0.001$) and that postinhalation scores were higher for panicking subjects than for nonpanicking subjects ($p<0.001$).

The repeated measures ANOVA performed on scores on the 10-point anxiety scale revealed a significant interaction of panic status and time. Again, this interaction demonstrated a differential change in anxiety scores over time on the basis of panic status, with subjects who panicked showing greater increases than those who did not. Post

TABLE 5. Change in Intensity of Panic Symptoms From Baseline to End of a 20-Minute Period of Inhalation of 7% CO₂ Among Subjects With Three Psychiatric Diagnoses and Normal Comparison Subjects Who Did and Did Not Panic in Response to the CO₂ Inhalation

Subject Group and Significant Group Comparison	Change in Score on Acute Panic Inventory					Change in Score on 10-Point Anxiety Scale					Change in Score on Borg Scale of Perceived Exertion (Breathlessness)				
	Mean	SD	F	df	p	Mean	SD	F	df	p	Mean	SD	F	df	p
Subject groups															
Panic disorder															
Panickers (N=32)	19.38	10.95				4.34	2.56				7.03	2.61			
Nonpanickers (N=16)	8.88	2.78				1.69	1.35				5.00	3.18			
Major depression															
Panickers (N=7)	21.29	7.52				4.43	2.23				6.29	2.22			
Nonpanickers (N=13)	8.23	5.23				1.54	1.20				4.00	2.52			
Premenstrual dysphoric disorder															
Panickers (N=5)	21.20	9.98				4.00	2.74				5.80	4.27			
Nonpanickers (N=4)	11.00	10.23				1.25	1.26				4.50	4.04			
Normal comparison subjects															
Panickers (N=5)	14.60	3.98				2.80	2.59				5.60	3.78			
Nonpanickers (N=27)	6.04	6.24				0.96	1.29				3.56	2.19			
Significant group comparisons															
Main effect of diagnostic group			7.90	3, 101	0.001 ^a										
Interaction of panic status and time ^b			28.73	1, 101	0.001 ^a			27.13	1, 101	0.001 ^a			7.69	1, 101	0.007 ^a

^a Significant at the <0.05 level (two-tailed test).^b End of the baseline period immediately before CO₂ inhalation versus end of the period of CO₂ inhalation.

hoc testing confirmed that subjects who panicked in response to 7% CO₂ had higher anxiety scores preinhalation than nonpanicking subjects ($p < 0.001$) and that postinhalation scores were higher for panicking subjects than for nonpanicking subjects ($p < 0.001$). Lack of a group interaction showed that although the increase in anxiety scores was greater in subjects who panicked, there were no differences in response between the diagnostic groups.

For the Borg breathlessness scale, the repeated measures ANOVA revealed the same significant interaction found for the Acute Panic Inventory and the 10-point anxiety scale: interaction of panic status and time. This interaction shows that panicking subjects reported greater increases in breathlessness than nonpanicking subjects. However, the lack of a group effect suggests that there were no differences among groups that could not be explained by panic. Post hoc analyses of the interaction of panic status and time showed that although panicking subjects did not differ significantly from nonpanicking subjects in preinhalation breathlessness scores, both groups reported significant increases in breathlessness in response to 7% CO₂ inhalation, with panicking subjects having significantly greater postinhalation breathlessness scores than nonpanicking subjects ($p < 0.001$).

In summary, rates of panic in response to both 5% and 7% CO₂ were significantly higher in panic disorder subjects than in normal comparison subjects, and the panic rates of the panic disorder group and the premenstrual dysphoric disorder group were not distinguishable. Panic disorder patients were distinguishable from depressed patients by their rates of panic in response to 5% CO₂, but not 7% CO₂, as revealed by conservative statistical testing

methods. In terms of intensity of behavioral response to 5% CO₂ and to 7% CO₂, as measured by the main outcome measure, the Acute Panic Inventory, panicking panic disorder subjects did not differ significantly from panicking subjects in the other groups. For the 10-point anxiety scale and the Borg breathlessness scale, three-way interactions showed that the most marked response to 5% CO₂ inhalation was among the small number of normal comparison subjects (N=3) who experienced panic attacks.

Comparison of Responses to 5% and 7% CO₂

To compare the ability of the different CO₂ concentrations (5% and 7%) to elicit panic attacks in each subject group, we performed separate exact binomial (McNemar) tests on the panic rates for the 5% and 7% CO₂ conditions as assessed by the blinded raters. For the panic disorder group, the panic rate in response to 5% versus 7% reached a significant level of difference ($p < 0.04$), with a higher percentage of panic disorder subjects panicking in response to 7% CO₂ than to 5% CO₂. There was no significant difference in the panic rates in response to 5% CO₂ and 7% CO₂ for the remaining three groups (depressed, premenstrual dysphoric disorder, or normal comparison), although a higher percentage of subjects panicked in response to 7% CO₂ in each group.

Discussion

In this study, part of a series of studies investigating the behavioral and respiratory responses of panic disorder patients to CO₂ challenge, we have replicated our own and others' findings of a greater anxiogenic effect of CO₂ inha-

lation on panic disorder subjects versus normal comparison subjects in a large, independent cohort. Confirming our hypothesis, depressed subjects proved to be largely resistant to the panicogenic effects of CO₂. This finding is consistent with that of Perna et al. (14), who found panic rates in response to CO₂ inhalation in subjects with major depression to be comparable to those in healthy subjects. These findings suggest that although panic disorder and major depression are highly comorbid, one physiologic means of distinguishing major depression from panic disorder may be by differences in panic response to CO₂ inhalation.

Although the data on panic rates in the premenstrual dysphoric disorder group must be interpreted cautiously due to the small sample size, the results for this group are in line with those of Harrison et al. (15), who found comparable CO₂ panic response rates in premenstrual dysphoric disorder and panic disorder populations. However, we were unable to confirm or reject our hypothesis that patients with premenstrual dysphoric disorder are distinguishable from patients with major depression on the basis of higher panic rates, due to a lack of sufficient statistical power. Another concern is that we did not perform the CO₂ tests on all subjects with premenstrual dysphoric disorder during the same phase of the menstrual cycle. Overall, however, these results lend support to the suggestion that the pathophysiology of premenstrual dysphoric disorder may be more similar to that of anxiety than to that of depression.

Our second hypothesis was confirmed by our findings that the characterization of the degree of the CO₂ response in terms of symptom intensity as measured by the Acute Panic Inventory was less dependent on diagnosis than on whether subjects panicked. It should be noted, however, that panic disorder subjects who panicked in response to 5% CO₂ inhalation were distinguishable from the other groups by their significantly higher baseline scores on the Acute Panic Inventory. However, their response to 5% CO₂ inhalation, as measured by the increase in the Acute Panic Inventory scores, was not distinguishable from that of panicking subjects in the other groups. It is interesting to note that on the secondary measures (the 10-point anxiety scale and the Borg breathlessness scale), the small number of panicking normal comparison subjects responded with anxiety and breathlessness equal to or greater than that of the panic disorder subjects. Of course, it is possible that some of the subjects who experienced a panic attack during the study may have latent panic disorder that was not yet clinically apparent. An alternate explanation is that the experience of having a first panic attack in subjects with no history of significant anxiety or panic attacks may evoke higher levels of symptoms on the basis of fear-evoking novelty alone. Overall, however, these data suggest that vulnerability to panic attacks crosses diagnostic groups and that once an attack is elicited, it is similarly expressed in most subjects.

Seven percent CO₂ was a more robust panicogen than 5% CO₂, and response to 7% CO₂ better differentiated panic disorder subjects from normal comparison subjects in terms of rates of panic (panic disorder subjects were the only group to demonstrate significantly higher panic rates in response to 7% CO₂ than in response to 5% CO₂). However, response to 7% CO₂ was less useful in distinguishing panic disorder subjects from depressed subjects.

In summary, the results support the idea that the rate of occurrence of panic attacks in response to CO₂, not the increase in the intensity of the symptoms, distinguishes panic disorder subjects. However, subjects with panic disorder who are vulnerable to CO₂-induced panic attacks are noted to have greater baseline anxiety than those who are not vulnerable and those in other diagnostic groups. Overall, subjects who experienced a panic attack in response to CO₂ reported similar symptom intensity, regardless of diagnosis, including the small number of normal comparison subjects. To differentiate patients with panic disorder from normal comparison subjects on the basis of rates of panic attacks, testing response to 7% CO₂ is superior to testing with 5% CO₂. This finding is supported by our previous work with 5% and 7% CO₂ concentrations (5). However, when comparing panic rates across clinical populations, testing with 7% CO₂ results in some loss of specificity, suggesting that testing with 5% CO₂ may be superior for this purpose. This report focused on panic rates and the quantitative behavioral response to CO₂ inhalation. Whether the qualitative nature of panic attacks, as defined by specific symptom clusters, is consistent across diagnostic groups is an important area for further investigation.

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