ORIGINAL ARTICLE

Differential Carbon Dioxide Sensitivity in Childhood Anxiety Disorders and Nonill Comparison Group

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Background: To examine the relationship between respiratory regulation and childhood anxiety disorders, this study considered the relationship between anxiety disorders and symptoms during carbon dioxide (CO_2) exposure, CO_2 sensitivity in specific childhood anxiety disorders, and the relationship between symptomatic and physiological responses to CO_2.

Methods: Following procedures established in adults, 104 children (aged 9-17 years), including 25 from a previous study, underwent 5% CO_2 inhalation. The sample included 57 probands with an anxiety disorder (social phobia, generalized anxiety disorder, separation anxiety disorder, and panic disorder) and 47 nonill comparison subjects. Symptoms of anxiety were assessed before, during, and after CO_2 inhalation.

Results: All children tolerated the procedure well, experiencing transient or no increases in anxiety symptoms. Children with an anxiety disorder, particularly separation anxiety disorder, exhibited greater changes in somatic symptoms during inhalation of CO_2-enriched air, relative to the comparison group. During CO_2 inhalation, symptom ratings were positively correlated with respiratory rate increases, as well as with levels of tidal volume, minute ventilation, end-tidal CO_2, and irregularity in respiratory rate during room-air breathing.

Conclusions: Childhood anxiety disorders, particularly separation anxiety disorder, are associated with CO_2 hypersensitivity, as defined by symptom reports. Carbon dioxide hypersensitivity is associated with physiological changes similar to those found in panic disorder. These and other data suggest that certain childhood anxiety disorders may share pathophysiological features with adult panic disorder.

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PANIC ATTACKS usually begin in adolescence and only occasionally evolve into full-blown panic disorder.[1-4] Family-based and longitudinal studies suggest that children at risk for panic disorder may exhibit a diathesis for the condition manifest as physiological abnormalities, particularly as respiratory dysregulation.[1-18] If so, research on respiratory correlates of childhood anxiety may clarify the relationship between childhood anxiety and adult panic disorder.

The association between panic disorder and heightened response to carbon dioxide (CO_2) inhalation is well documented. During CO_2 inhalation, patients with panic disorder report more anxiety and dyspnea than comparison subjects,[19-28] a characteristic known as *CO_2 hypersensitivity*. This type of CO_2 hypersensitivity is selectively reduced by treatments that are effective in panic disorder[19,23,24] and is associated with specific physiological abnormalities.[20,29] While CO_2 hypersensitivity is typically found in panic disorder, it also occurs selectively in other conditions, such as isolated panic attacks, that are closely related to panic disorder.[25-30] Similarly, nonill first-degree relatives of patients with panic disorder also show signs of CO_2 hypersensitivity.[16,18]

These findings suggest that CO_2 hypersensitivity characterizes a spectrum of syndromes related to adult panic disorder and possibly including childhood anxiety disorders. For example, children of adults with panic disorder experience elevated rates of separation anxiety disorder,[5,15] behavioral inhibition,[6] and overanxious disorder.[11] Similarly, panic disorder is often preceded by separation anxiety disorder, isolated panic attacks, or overanxious disorder.[2,4,12-14] These findings suggest that, as in adult panic disorder, some childhood anxiety disorders may be characterized by CO_2 hypersensitivity. This hypothesis was supported by recent preliminary results.[31]

That initial study used a single index of CO_2 hypersensitivity in a small sample of anxious and comparison chil-

SUBJECTS AND METHODS

SUBJECTS

Probands included 57 children aged 9 to 17 years with a current *DSM-IV*[32] anxiety disorder; the comparison group included 47 subjects without any current *DSM-IV* disorder. Of the 104 subjects, 25 had been included in a previous report from our group.[31] Data from the additional 79 subjects have not been reported previously.

Probands were recruited when they sought treatment for an anxiety disorder. Five additional probands as well as 22 comparison subjects were recruited from an epidemiological study; an additional 25 comparison subjects were recruited through advertisement. To obtain subjects from the epidemiological sample, we contacted 40 consecutive families, randomly selected from households containing 9- to 17-year-olds by means of census tracts.

Anxiety disorders included separation anxiety disorder (n=25), generalized anxiety disorder (n=29), panic disorder (n=9), and social phobia (n=26) (**Table 1**). Cases of overanxious disorder, diagnosed before 1994, were reclassified as generalized anxiety disorder, given the strong overlap between the 2 conditions.[2] All subjects were medically healthy and medication free for at least 2 weeks before participation. The total number of anxiety diagnoses exceeds the number of probands because of comorbidity. There were 33 cases with an isolated or "pure" form of anxiety disorder. The association between CO_2 sensitivity and specific anxiety disorders is examined among these pure cases.

Procedures were approved by the institutional review board of New York State Psychiatric Institute, New York. Families were informed that this was not a treatment study and that some transient distress was possible. Parents provided signed informed consent, and children provided assent.

PSYCHIATRIC ASSESSMENT

Subjects were examined for psychopathological characteristics by means of either the Diagnostic Interview Schedule for Children[33] or the Parent Respondent Interview Schedule,[34] as outlined by Pine et al.[31] Interviews were administered by experienced clinicians (D.S.P., R.G.K., and others) with master's or higher-level degrees. The use of 2 instruments was unavoidable, since participants were selected from either a research clinic or an ongoing epidemiological study, settings that required different standardized interviews. On the day of the procedure, a psychiatrist (D.S.P. and others) or clinical psychologist reviewed children's symptoms with the child and parent to confirm the presence of anxiety disorders. Diagnoses were made without exclusionary criteria, and no effort was made to define any anxiety disorder as "primary."

LABORATORY PROCEDURES

The possibility of developing anxiety while breathing CO_2-enriched air was discussed with families at recruitment and again immediately before the procedure. Children were instructed to signal if they felt uncomfortable or if they wished to stop the procedure for any reason. A technician and a physician remained with the child at all times, reminding the child to signal if he or she wished to terminate the procedure. Children could see staff and communicate readily with them, both verbally and through hand gestures. Parents remained in an adjacent room approximately 3 m from their child but could be in the room if either they or the child requested. Children lay in a plastic canopy they could exit by lifting a latch (see Pine et al[31] for details). Fifteen minutes of room-air breathing was followed by 15 minutes of 5% CO_2 inhalation. Parents and children were blind to the timing of CO_2 breathing. As in the previous report by our group,[31] tidal volume, minute ventilation, and respiratory rate were measured by spirometry; end-tidal CO_2 was monitored by capnography. Baseline values were averaged for the 15-minute baseline. The CO_2-induced changes in respiration were averaged across 2-minute periods.

ASSESSMENT OF CO_2 HYPERSENSITIVITY

Panic symptoms were rated on the Acute Panic Inventory (API) modified for children[31]; dyspnea was rated on the Borg scale[20]; and state anxiety was rated by means of a 10-point

Continued on next page

dren (n=25). The current study expands the sample and uses 4 measures of CO_2 hypersensitivity. Moreover, based on longitudinal and family data linking separation anxiety and generalized anxiety disorders to adult panic disorder, the study tests the hypothesis that CO_2 hypersensitivity relates primarily to these 2 conditions and not social phobia.[2,5,11-15] Finally, the current study tests the hypothesis that CO_2 hypersensitivity in children relates to abnormalities in respiratory physiological characteristics associated with panic disorder.

RESULTS

SAMPLE CHARACTERISTICS

Table 1 summarizes sample characteristics. Because of a trend for probands and comparison subjects to differ on height and age, these variables are controlled in the analyses.

PANIC RATING

Of 56 probands, 19 (34%) met criteria for CO_2-induced panic vs 1 (2%) of 47 comparison subjects ($\chi^2=18.2$; $P<.001$). A logistic regression model was fit including any diagnosis vs no diagnosis as a predictor, controlling for age, sex, and the preinhalation score on the API. Models were also fit including preinhalation anxiety or dyspnea ratings as predictors, but a model could not be fit including more than 1 preinhalation scale score because of multicollinearity. Panic ratings were predicted by diagnosis in all models, but not by age, sex, or any scale rating. With a model including age, sex, and the API score, anxiety diagnosis was the only predictor of CO_2-induced panic (odds ratio, 17.8; 95% confidence interval, 2.2-147; Wald $\chi^2=7.2$; $P=.008$).

Examination of specific diagnostic predictors for CO_2-induced panic was restricted to the 47 comparison

analog scale. Immediately before the procedure, each scale question was reviewed with the child to ensure that questions were understood.[31] As in previous studies, a panic attack was defined as the development of crescendo anxiety with fear and at least 4 somatic symptoms. This rating was made by an experienced rater (J.M.M.) without awareness of the child's diagnosis, on the basis of the child's ratings as well as nonverbal signs of anxiety.

Symptom ratings were made after 15 minutes of room-air breathing and at the end of the CO_2 inhalation epoch, which occurred either at 15 minutes or at the point when a child asked to stop breathing CO_2. To make ratings at these time points, the blind rater posed specific questions to children, who responded verbally or by pointing to answers on a chart.

ASSESSMENTS AFTER STUDY PROCEDURE

To determine the duration of any increase in anxiety and to determine whether anxiety symptoms developed after the procedure, all children were reassessed systematically by a nonblind study psychiatrist (D.S.P.) approximately 15 minutes after the CO_2 inhalation procedure. Attempts were made to repeat such assessments within 1 month of study participation and 1 to 3 years later. At these repeated assessments, a parent was interviewed systematically, directly if possible or by telephone by the study psychiatrist (D.S.P.), about the child's experience during and subsequent to the procedure.

DATA ANALYSIS

Data were analyzed for the entire sample and separately for the 79 new participants. Since these analyses generated the same conclusions, results for the entire sample are reported.

As in adult studies, CO_2 hypersensitivity was defined by means of 4 symptom-based indexes: API, state anxiety, Borg dyspnea, and rater-designated panic attack ratings. Bivariate associations were examined with *t* tests, continuity-corrected χ^2, or Fisher exact test. Associations with multiple predictors were examined by logistic regression for panic attack ratings; multiple linear regression for API, state anxiety, and Borg ratings; or repeated-measures analysis of covariance for physiological variables. Measures of variability in physiological variables over time relied on the within-subject SD. In linear regression models, each rating scale score during CO_2 inhalation was regressed on the baseline score for that same scale so that regression coefficients modeled the change for each scale. Symptom scale ratings were highly intercorrelated at baseline and during CO_2 inhalation. As a result, regression models were complicated by multicollinearity if more than 1 predictor scale was included. Ratings for a given scale during CO_2 inhalation correlated most strongly with baseline ratings for that same scale. Therefore, each scale rating during CO_2 inhalation was regressed on the baseline rating for that same scale but no other scale ratings. Logistic regression was used to examine diagnostic specificity in panic attack ratings, entering individual anxiety diagnoses as predictors of CO_2-induced panic, including only pure cases.

Data were removed from group comparisons of physiological variables for 10 subjects (6 probands and 4 comparison subjects) who asked to stop the procedure within 2 minutes. As has been the case in adult studies, too many participants ended the procedure after 4 minutes to provide meaningful comparisons beyond this point.

Baseline group differences were tested by analysis of covariance. During CO_2 inhalation, main effects of group and time, as well as group × time interactions, were tested by repeated-measures analysis of covariance, controlling for height and sex. Hypotheses on differential CO_2 sensitivity are supported by group × time interactions. Since age and height are highly correlated, they are not entered simultaneously because of multicollinearity. Exploratory analyses examined associations between respiratory and symptomatic indexes at baseline, between respiration at baseline and symptom changes during CO_2 inhalation, and between symptoms at baseline and respiratory changes during CO_2 inhalation.

To determine statistical significance, a 2-tailed $\alpha = .05$ was chosen for a priori hypotheses. Bonferroni correction was used for other analyses that involved multiple comparisons in the absence of a priori hypotheses.

subjects and 30 probands with pure anxiety disorders, including 10 with social phobia, 10 with separation anxiety disorder, and 10 with generalized anxiety disorder. Panic disorder was excluded because of the scarcity of pure cases (n=3). Separation anxiety disorder emerged as the only significant predictor of CO_2-induced panic (**Table 2**).

SYMPTOM SCALES

Between-group differences on symptom scales were tested with 2-tailed *t* tests, considering $P = .002$ as statistically significant. This represents a Bonferroni-corrected value for the total number of tests in **Table 3** (0.05/24). This threshold was selected because of limited evidence from adult studies of specificity in the association between anxiety disorders and one or another symptomatic index of CO_2 hypersensitivity. As a group, probands significantly differed from comparison subjects on anxiety and API ratings, both at baseline and during CO_2 inhalation (Table 3). Symptom levels during CO_2 inhalation returned to baseline levels shortly after termination of CO_2 inhalation, and no child reported any increase in symptoms after termination of CO_2 inhalation. None of the scale score differences between narrowly defined diagnostic groups and healthy comparisons met the $P = .002$ criterion. This lack of between-group differences should be interpreted cautiously, given low statistical power with the conservative statistical threshold.

Three linear regression models, using pure cases, examined changes on the API, the anxiety scale, and the Borg dyspnea scale during CO_2 inhalation as a function of diagnostic status. These models rely on $P = .02$ (0.05/3) to correct for multiple comparisons. Scale scores during CO_2 inhalation were regressed on the baseline score for that scale, as well as age, sex, and dummy variables for

Table 1. Sample Characteristics*

Characteristic	Comparison Group (n = 47)	Proband Group (n = 57)	Statistic, Group Contrast
Age, mean ± SD, y	13.4 ± 2.5	12.5 ± 2.7	t_{102} = 1.7
Sex, No. (%) F	23 (49)	24 (42)	χ^2 = 0.5
Height, mean ± SD, cm	159.3 ± 10.9	154.0 ± 14.5	t_{102} = 2.0†
Weight, mean ± SD, kg	54.1 ± 14.9	59.4 ± 23.6	t_{102} = 1.3
Generalized anxiety disorder, No.	NA		NA
Total		27	
Pure cases‡		10	
Only GAD and SAD		6	
Only GAD and SOPH		5	
≥3 Anxiety disorders		6	
Separation anxiety disorder, No.	NA		NA
Total		25	
Pure cases		10	
Only SAD and SOPH		6	
≥3 Anxiety disorders		3	
Social phobia, No.	NA		NA
Total		24	
Pure cases		10	
≥3 Anxiety disorders		3	
Panic disorder, No.	NA		NA
Total		9	
Pure cases		3	
2 Anxiety disorders		4	
≥3 Anxiety disorders		2	

*GAD indicates generalized anxiety disorder; SAD, separation anxiety disorder; SOPH, social phobia; and NA, not applicable.
†P≤.05.
‡"Pure cases" refers to cases with only 1 anxiety disorder.

each of the 3 anxiety disorders. During CO_2 inhalation, separation anxiety disorder was associated with significant increases in anxiety, API, and dyspnea ratings (**Table 4**). Generalized anxiety disorder was associated with an increase in anxiety but not API or dyspnea ratings. No other associations emerged in these analyses.

RESPIRATORY PHYSIOLOGICAL FINDINGS

Physiological profiles were contrasted among 3 groups with the use of P=.05 for statistical significance in view of the extensive data among adults that foster a priori hypotheses. Adults who develop symptoms of panic during CO_2 inhalation consistently exhibit enhanced respiratory rate responses to CO_2 and elevated mean tidal volume or minute ventilation during room-air breathing. For the current study, the 3 groups were composed of the healthy comparison subjects and the probands who did and who did not develop CO_2-induced panic. This excludes the lone comparison subject who met criteria for CO_2-induced panic.

The groups differed on baseline tidal volume ($F_{2,127}$=3.4; P<.01; **Table 5**) because of significantly greater tidal volume in probands who developed panic symptoms compared with healthy comparison subjects (t_{68}=2.5; P<.01). As hypothesized, there was a significantly steeper increase in respiratory rate during CO_2 inhalation for probands who experienced panic symptoms, relative to comparison subjects (Table 5).

Table 2. Predictors of Carbon Dioxide–Induced Panic Ratings (N = 77)*

Predictor Variables	Odds Ratio (95%, CI)	Wald χ^2
5-y Increase in age	0.4 (0.1-2.8)	0.9
Female sex	2.6 (0.3-20.1)	0.9
Baseline API rating	1.7 (0.6-5.1)	1.0
SAD diagnosis	44.7 (3.3-661)	11.1†
GAD diagnosis	7.2 (0.5-99)	2.1
SOPH diagnosis	3.3 (0.2-74)	0.8

*A logistic regression model is fit with the use of only pure cases (n = 30) and comparison subjects (n = 47). All 6 predictor variables are entered in 1 model. API indicates Acute Panic Inventory score; SAD, separation anxiety disorder; GAD, generalized anxiety disorder; and SOPH, social phobia.
†P=.005.

In post hoc analyses, probands with panic symptoms differed both from healthy participants ($F_{2,110}$=5.4; P=.004) and probands without panic disorder ($F_{2,94}$=4.8; P=.009). Both interactions reflected the steeper increase in the group reporting panic symptoms. A significant group×time interaction for tidal volume also emerged. However, unlike respiratory rate response, a steeper tidal volume response occurred in probands who did not meet criteria for panic, relative to comparison subjects. In post hoc analyses contrasting the probands without panic disorder with the other 2 groups, there were significant group×time interactions, indicating steeper responses compared with healthy comparison subjects ($F_{2,154}$=6.3; P=.002) and probands reporting panic symptoms ($F_{2,98}$=3.4; P=.04).

In addition, across the 15 minutes of room-air breathing before CO_2 inhalation, probands reporting panic symptoms had significantly more irregularity in respiratory rate (t_{65}=2.2; P=.02), manifested as higher average within-subject SDs, than did healthy comparison subjects (4.7±3.5 vs 3.8±1.6 breaths per minute, respectively). Probands without panic disorder did not differ from the other 2 groups. While breathing room air, comparison subjects and probands reporting panic symptoms did not differ on mean end-tidal CO_2 values (39.3±5.2 vs 39.8±3.5 mm Hg, respectively).

Finally, we conducted exploratory analyses on relationships among symptom ratings and physiological findings. Given the number of statistical tests, coupled with their exploratory nature, results are reported only for 2-tailed P<.005. Higher dyspnea ratings at baseline predicted enhanced respiratory rate responses to CO_2 at 4 minutes (t_{89}=4.2; P<.001). Furthermore, higher baseline minute ventilation predicted greater increase in anxiety during CO_2 inhalation (t_{94}=2.93; P=.004). Finally, both lower end-tidal CO_2 (t_{93}=3.1; P=.002) and higher minute ventilation (t_{94}=3.0; P=.004) predicted significantly greater increases in API scores during CO_2 inhalation.

POSTSTUDY STATUS

We systematically reinterviewed 92 (88%) of 104 parents at follow-up. In 64 participants, we obtained

Table 3. Symptom Scores Immediately Before and During Carbon Dioxide Inhalation in Children With Anxiety Disorders and Comparisons*

		All Probands (n = 57)		Pure SAD (n = 10)		Pure GAD (n = 10)		Pure SOPH (n = 10)	
	Comparison Group (n = 47), Mean ± SD	Mean ± SD	Group Contrast†	Mean ± SD	Group Contrast†	Mean ± SD	Group Contrast†	Mean ± SD	Group Contrast†
Anxiety‡									
Pre-CO_2	1.2 ± 0.5	2.0 ± 1.3	$t_{60.8} = 3.3$§	2.5 ± 2.5	$t_{9.1} = 1.7$	1.8 ± 1.2	$t_{9.5} = 1.6$	1.8 ± 1.7	$t_{10.4} = 1.2$
During CO_2	2.1 ± 1.9	4.2 ± 3.3	$t_{65.8} = 4.6$§	5.1 ± 3.9	$t_{9.5} = 2.5$	4.8 ± 3.1	$t_{9.7} = 2.9$	2.6 ± 2.7	$t_{11.3} = 0.7$
API									
Pre-CO_2	1.3 ± 1.7	5.0 ± 8.0	$t_{61.1} = 3.3$§	8.0 ± 10.2	$t_{9.1} = 2.1$	5.7 ± 6.1	$t_{9.3} = 2.3$	2.1 ± 4.1	$t_{10.9} = 0.6$
During CO_2	3.6 ± 3.0	9.8 ± 9.6	$t_{73.4} = 4.5$§	15.1 ± 12	$t_{9.3} = 3.0$	11.7 ± 8.7	$t_{9.4} = 2.9$	6.2 ± 9.3	$t_{10.5} = 0.9$
Dyspnea‖									
Pre-CO_2	0.30 ± 0.9	0.9 ± 1.9	$t_{81.6} = 2.2$	0.7 ± 1.6	$t_{10.3} = 0.7$	1.6 ± 1.9	$t_{9.8} = 2.1$	0.4 ± 1.2	$t_{58} = 0.2$
During CO_2	1.7 ± 2.0	3.3 ± 3.4	$t_{89.8} = 2.8$	5.3 ± 4.1	$t_{10.1} = 2.6$	3.8 ± 3.1	$t_{10.7} = 2.0$	1.8 ± 1.9	$t_{58} = 0.1$
Panic rate¶	1/47	19/57	$\chi^2 = 15.0$§	6/10	FET§	2/10	FET	1/11	FET

*API indicates Acute Panic Inventory score; SAD, separation anxiety disorder; GAD, generalized anxiety disorder; SOPH, social phobia; and FET, Fisher exact test. Degrees of freedom on t tests reflect adjustment for unequal variances when between-group variance differences are found (P<.05).

†All contrasts are with comparison group.

‡Anxiety is rated with a visual analog scale. A higher score indicates greater anxiety.

§P≤.001.

‖Dyspnea is measured with the Borg scale.

¶Panic is rated by the blind observer (J.M.).

Table 4. Predictors of Carbon Dioxide–Induced Anxiety and Somatic Symptoms*

	Symptom Scale Ratings During CO_2 Inhalation					
	API		Anxiety§		Dyspnea‖	
Predictor Variables	OR† (95% CI)	t_{71}‡	OR† (95% CI)	t_{71}‡	OR† (95% CI)	t_{71}‡
Age	0.99 (0.95-1.0)	0.8	1.1 (1.0-1.2)	0.1	1.1 (0.99-1.1)	1.5
Sex	1.0 (0.81-1.3)	0.3	1.4 (0.89-2.1)	1.5	1.2 (0.84-1.6)	0.8
Baseline API score¶	2.8 (2.3-3.4)	10.2#	NA	NA	NA	NA
Baseline anxiety score¶	NA	NA	2.5 (1.7-3.7)	4.3#	NA	NA
Baseline dyspnea score¶	NA	NA	NA	NA	1.7 (1.3-2.1)	4.6#
SAD	1.6 (1.1-2.4)	2.2**	2.1 (1.2-3.5)	2.7**	3.1 (1.9-5.2)	4.3#
GAD	1.5 (1.0-2.2)	1.9	2.3 (1.4-3.8)	3.2**	1.4 (0.81-2.3)	1.2
SOPH	1.2 (0.85-1.8)	1.1	0.76 (0.53-1.1)	1.4	0.9 (0.48-1.7)	0.4

*Variables at the top of each column are regressed on all predictors by linear regression. Variables with cells marked NA were not entered in the regression equation. Only pure cases are included in these analyses. API indicates Acute Panic Inventory Score; OR, odds ratio; CI, confidence interval; SAD, separation anxiety disorder; GAD, generalized anxiety disorder; SOPH, social phobia; and NA, not applicable.

†Odds ratio with 95% CI is generated from multivariate equation, such that 1 unit of increase for continuous scales, or a positive rating for dichotomous diagnostic indicators, predicts risk for 1-SD increase in dependent measure.

‡The t value represents t test on the regression coefficient.

§Anxiety is measured with a visual analog scale. A higher score indicates greater anxiety.

‖Dyspnea is measured with the Borg scale.

¶Variable is standardized, such that OR is for 1-SD change in dependent measure associated with a 1-SD increase in the independent measure.

#P≤.001.

**P≤.01.

information covering 1 to 3 years after participation. In 28 participants, information was available only for the period immediately after participation. In no child was there a report of exacerbation of ongoing anxiety, emergence of new anxiety symptoms related to participation, or report of new-onset panic disorder. Parents of children who had become anxious during participation recalled the child having felt anxious, but only transiently, consistent with observations made during the study. Similarly, for children who did not report feeling anxious at participation, the procedure was not recalled by parents as anxiety provoking.

COMMENT

The current study documents a relationship between respiratory dysregulation and childhood anxiety disorders. Evidence of symptomatically defined CO_2 hypersensitivity was clearly present for separation anxiety disorder; it was present to a lesser degree in generalized anxiety disorder; but it was absent in social phobia. Among children with anxiety disorders, subjective signs of CO_2 hypersensitivity, including anxiety and dyspnea at baseline as well as symptom increases during CO_2 inhalation, were associated with abnormalities in respiratory

Table 5. Physiological Response to Carbon Dioxide in Probands and Comparison Group

Physiological Measure	Group, Mean ± SD			Statistics*
	Comparison	Proband, No Panic	Proband, Panic	
Respiratory frequency, breaths/min				
Baseline	20.8 ± 3.8	21.3 ± 4.5	21.6 ± 4.5	$F_{2,127} = 0.1$
Carbon dioxide				
1 min	21.0 ± 4.9	21.1 ± 4.9	21.8 ± 5.3	G: $F_{2,89} = 0.6$; T: $F_{1,89} = 3.8$; G × T: $F_{2,89} = 5.1$†
2 min	21.2 ± 5.4	21.2 ± 5.1	22.3 ± 5.1	
3 min	21.9 ± 5.6	22.6 ± 6.0	25.5 ± 6.2	
4 min	22.3 ± 5.4	22.5 ± 6.5	26.8 ± 7.4	
Tidal volume, mL				
Baseline	191.6 ± 84.6	202.6 ± 81.6	232.0 ± 127.2	$F_{2,127} = 3.4$‡
Carbon dioxide				
1 min	235.9 ± 98.3	251.6 ± 99.5	249.8 ± 100.6	G: $F_{2,89} = 3.8$‡; T: $F_{1,89} = 6.1$†; G × T: $F_{2,89} = 4.3$†
2 min	343.3 ± 122.9	380.5 ± 156.8	384.1 ± 169.3	
3 min	429.3 ± 144.1	476.9 ± 201.5	441.3 ± 192.5	
4 min	479.1 ± 168.4	550.0 ± 243.3	474.6 ± 206.8	
Minute ventilation, L/min				
Baseline	3.89 ± 1.71	4.17 ± 1.71	4.79 ± 2.62	$F_{2,127} = 2.6$
Carbon dioxide				
1 min	4.80 ± 1.95	5.08 ± 1.82	5.49 ± 2.83	G: $F_{2,89} = 1.8$; T: $F_{1,89} = 0.4$; G × T: $F_{2,89} = 1.3$
2 min	7.09 ± 2.72	7.80 ± 3.21	8.37 ± 4.07	
3 min	9.27 ± 3.47	10.36 ± 3.90	10.87 ± 4.91	
4 min	10.62 ± 4.53	11.89 ± 5.46	12.33 ± 5.82	

**G indicates effect of group on physiological measure in repeated-measures analysis of variance (ANOVA) during carbon dioxide (CO_2) inhalation; T, effect of time on physiological measure in repeated-measures ANOVA during CO_2 inhalation; and G × T, group × time interaction for physiological measure in repeated-measures ANOVA during CO_2 inhalation.*

†P<.01.

‡P<.05.

physiological profiles, findings characteristic of adult panic disorder. These abnormalities include an enhanced respiratory rate response during CO_2 breathing, as well as elevated minute ventilation and lower end-tidal CO_2 during room-air breathing.

Panic induced by CO_2, as an index of CO_2 hypersensitivity, is more frequent in adult panic disorder (50%-80%) than in children with anxiety disorders (30%-60%). There are several potential explanations for this difference. Cognitive maturation might affect symptom reporting during CO_2 exposure.[1] Alternatively, maturation of biological systems involved in anxiety could influence rates of both natural and CO_2-induced panic. There is some evidence of relatively late maturation of the noradrenergic as opposed to the serotonergic system.[35] Late maturation of the noradrenergic system and lower rates of CO_2-induced panic in children would be consistent with evidence of noradrenergic involvement in both spontaneous panic and respiratory control.[36-38]

The current data indicate that the study of respiratory regulation through the CO_2 inhalation procedure is relevant to an understanding of physiological mechanisms in anxiety states across development. Inhalation of CO_2 is well tolerated. In the children studied, CO_2-associated anxiety was uniformly transient, as demonstrated by follow-up interviews. It occurs in select children, 95% of whom have clinically impairing anxiety.

The absence of an association between CO_2 sensitivity and childhood social phobia is consistent with longitudinal and family-based studies finding no association between childhood social phobia and adult panic disorder.[2,39] Nevertheless, childhood social phobia is often comorbid with separation anxiety or generalized anxiety disorder,[40] and comorbid forms of social phobia have a more consistent association with panic disorder.[41] Therefore, it is important to distinguish pure from comorbid forms of childhood social phobia. Conversely, both probands with separation anxiety and those with generalized anxiety disorders showed enhanced anxiety responses to CO_2 compared with nonill peers (Table 4). Separation anxiety disorder was specifically associated with panic and dyspnea in response to CO_2. These findings are consistent with family-based and longitudinal studies linking separation anxiety disorder to adult panic disorder.[2,5,12,13] These results are also consistent with previous findings of associations among childhood respiratory illness, separation anxiety disorder, and adult panic disorder.[42,43] Childhood generalized anxiety disorder also predicted an increase in anxiety ratings during CO_2 inhalation. While these data are consistent with longitudinal and family studies in children,[2,11] they are inconsistent with adult studies where generalized anxiety disorder is associated with normal CO_2 sensitivity.[44,45] This discrepancy may reflect the fact that only a minority of children with generalized anxiety disorder are at risk for adult panic disorder.[2] Studies of CO_2 hypersensitivity in adult generalized anxiety disorder exclude individuals with a childhood history of generalized anxiety disorder that evolved into panic disorder. Nevertheless, previous studies in adult generalized anxiety disorder, as in pediatric generalized anxiety disorder, have found patients to react to respiratory stimulants with high levels of anxiety but not dyspnea, relative to comparisons.[46]

Taken together, these findings on CO_2 hypersensitivity suggest that similar mechanisms may play a role in specific forms of both childhood and adult anxiety disorders. Both children with separation anxiety disorder and adults with panic disorder display particularly enhanced sensitivity to respiratory stimulation. If confirmed, these findings could carry important preventive and treatment implications. For example, sensitivity to respiratory stimulation may identify children at high risk for panic attacks during adulthood. Similarly, treatments that specifically target respiratory hypersensitivity, possibly by encouraging habituation to internal somatic cues, may prove effective in separation anxiety disorder.

The validity of children's subjective ratings of CO_2-induced anxiety is supported by the respiratory physiological data, since significant associations were noted between symptomatic measures of CO_2 hypersensitivity and signs of physiological dysregulation, as previously noted in adults. In adults, respiratory abnormalities occur primarily in patients with panic disorder who develop anxiety symptoms during CO_2 inhalation.[20,29] Five physiological abnormalities have been reported with varying consistency. An enhanced respiratory rate response to CO_2 stands as the most consistent CO_2-induced physiological abnormality in adult panic disorder.[20,22,29,47-49] During room-air breathing, low levels of end-tidal CO_2 and increased variability in respiratory measures represent the 2 most frequently noted abnormalities.[20,22,29] Finally, elevated mean levels of tidal volume and minute ventilation have been reported in panic disorder, during room air breathing, CO_2 inhalation, and spontaneous panic.[20,22] However, these findings are relatively less consistent.

Evidence of each physiological abnormality in children with anxiety disorders was obtained in the current study. Probands who developed panic symptoms exhibited significantly enhanced respiratory rate increases in response to CO_2, as well as increased variability in respiratory rate and elevated mean tidal volume during room-air breathing. Although we did not observe reduced end-tidal CO_2 levels in probands who developed panic symptoms during CO_2 inhalation, low levels of baseline end-tidal CO_2, as well as high levels of baseline minute ventilation, predicted response on symptom scales to CO_2. The finding of relatively increased tidal volume responses to CO_2 in probands who did not meet criteria for panic requires replication to interpret its significance, in view of inconsistent findings for this measure in adult panic disorder.

The current study has several limitations. First, more study of diagnostic specificity is required, since the number of cases with pure, specific childhood anxiety disorders was low. Second, conclusions on the specific role of CO_2 hypersensitivity are limited, since generalized sensitivity to stress in childhood anxiety cannot be ruled out. Children with anxiety disorders or children at risk for panic disorder have been shown to exhibit heightened reactivity to a range of mildly stressful experiences, including novelty or anticipation of mildly aversive events.[7,9,10] The current study considered only 1 type of stress. Some childhood anxiety disorders might be associated with heightened sensitivity to a range of stressors; others could have specific sensitivity to CO_2 inhalation. Finally, there is minimal knowledge of specific neural circuits across development that mediate various forms of stress reactivity, including respiratory responses to stress.[50-53]

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