ORIGINAL ARTICLE

Ventilatory Physiology of Children and Adolescents With Anxiety Disorders

Daniel S. Pine, MD; Jeremy D. Coplan, MD; Laszlo A. Papp, MD; Rachel G. Klein, PhD; Jose M. Martinez, MA; Pavel Kovalenko, PhD; Nancy Tancer, MD; Donna Moreau, MD; Eldon S. Dummit III, MD; David Shaffer, MD; Donald F. Klein, MD; Jack M. Gorman, MD

Background: Abnormalities in ventilatory physiology have been noted in adults with panic disorder. We tested the hypothesis that abnormalities in ventilatory physiology differentiate children and adolescents with anxiety disorders from psychiatrically healthy children.

Methods: Ventilatory physiology was monitored with a canopy apparatus during room-air breathing and 15 minutes of carbon dioxide exposure in 33 children and adolescents comprising 18 probands with an anxiety disorder and 15 psychiatrically healthy children.

Results: During room-air breathing, probands had significantly larger minute ventilation, larger tidal volumes, and more variable breathing patterns than healthy comparisons, but the groups did not differ in end-tidal carbon dioxide or respiratory rate. During carbon dioxide challenge, probands exhibited larger minute ventilation and respiratory rate responses relative to comparisons.

Conclusion: These findings on the association between ventilatory physiology and anxiety disorders in children and adolescents are consistent with results from studies of adults with panic disorder.

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From the New York State Psychiatric Institute and Columbia University, New York.

LEADING THEORIES view spontaneous panic attacks as alarm reactions triggered by cues of impending suffocation.[1-3] This view partly emanated from the observation that adults with panic disorder exhibit more anxiety and dyspnea than healthy comparisons during carbon dioxide (CO_2) challenge,[4-11] a procedure that physiologically simulates suffocation. Abnormalities in the neural control of breathing may account for CO_2 hypersensitivity.[1-3] Signs of abnormal respiratory control are found in patients with panic disorder during room-air breathing and CO_2 challenge.[12-21] These signs include room-air hyperventilation and variable breathing,[1-3,15,19-21] as well as enhanced respiratory rate responses to CO_2 exposure.[1-3,12-17] Although not all studies note the findings,[11,18] considerable evidence suggests there is an association between panic disorder and abnormal respiratory control.

Research about the ventilatory physiology of patients with anxiety disorders has been restricted to adults. While observations from retrospective and family studies[22-28] suggest that respiration may also play a role in childhood anxiety disorders, there is minimal direct research on this topic.[27] We recently compared rates of anxiety symptoms in children with 2 respiratory illnesses—asthma and congenital central hypoventilation syndrome—with rates in healthy comparisons.[28] Congenital central hypoventilation syndrome renders children physiologically insensitive to CO_2 exposure and incapable of experiencing dyspnea, suggesting incapacity for monitoring suffocation cues.[2] The study found increased anxiety in children with asthma but not in children with congenital central hypoventilation syndrome, suggesting a role for suffocation cues in childhood anxiety.

The present study compares the ventilatory physiology of children and adolescents with anxiety disorders with that of psychiatrically healthy children and adolescents. To facilitate comparison with data obtained in adults, subjects were evaluated using CO_2 challenge techniques identical to those used in earlier studies of panic disorder.[15] We include 3 disorders besides panic disorder: social phobia, separation anxiety, and overanxious disorder. The decision to include these disorders was based on 4 considerations: (1) the frequent comorbidity among children with anxiety disorders[29]; (2) the low rate of panic but high rate of anxiety during child-

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SUBJECTS AND METHODS

SUBJECTS

Study participants included 20 probands aged 7 to 16 years seeking treatment at an anxiety disorder clinic for anxiety disorders that meet the criteria of the *DSM-III-R*[31] (**Table 1**).

Fifteen comparisons without lifetime histories of psychiatric disorders were recruited to the study through advertisements. Comparisons were limited to children aged 9 years and older to prevent potentially adverse novel experiences in younger volunteers; therefore, age matching was precluded. All subjects were medication free and medically healthy.

PSYCHIATRIC ASSESSMENT

Subjects were evaluated through parent interviews by 1 of 3 clinicians using either the Diagnostic Interview Schedule for Children[32,33] or the Parent As Respondent Informant Schedule.[34] Direct interviews with children aged 9 years and older were also conducted using one of these 2 instruments. Both interviews have acceptable interrater and test-retest reliability.[32-34] Full diagnostic criteria for a current anxiety disorder had to be met using data from 1 informant, either the child or the parent, for probands to enter the study. All comparisons were evaluated with the Parent As an Informant Schedule to provide lifetime ratings, which are not provided by the Diagnostic Interview Schedule for Children. More than 1 instrument was used with probands since probands participated in various research protocols, some requiring the Diagnostic Interview Schedule for Children and others requiring the Parent As an Informant Schedule. It was not feasible to administer both interviews.

All probands, comparisons, and their parents were clinically interviewed by 1 of 3 child psychiatrists (D.S.P., N.T., or E.S.D.) after the standardized interviews. Psychiatrists confirmed either the presence of diagnostic criteria elicited during standardized interviews in patients or the absence of psychiatric disorders in comparisons. Probands entered the study only if both the standardized instrument and the psychiatrist elicited criteria for an anxiety disorder. Comparisons entered the study only if the instrument and the psychiatrist confirmed the absence of all disorders. Final diagnostic decisions for specific current diagnoses were made using best-estimate procedures,[35] with no knowledge of the physiological data, using all information, including standardized and clinical interviews.

CHALLENGE PROCEDURES

The study was approved by the institutional review board at New York State Psychiatric Institute, New York, NY. Parents provided consent; children provided assent. The study used 4 tests: a mental arithmetic test, followed by orthostatic challenge, and then CO_2 challenge (3 hours on day 1, with approximately 15 minutes between tests) and clonidine hydrochloride challenges that occurred on day 2. This report examines CO_2 challenge responses.

A technician (J.M.M.) and a physician (D.S.P. or E.S.D.) remained with the children at all times, providing reassurance during CO_2 challenge procedures. Parents remained in adjacent rooms, approximately 300 cm from the children. Parents could see and hear the children during CO_2 challenge; children could hear but not see their parents (because of positioning). Parents were allowed to be in the room if the child requested their presence; one 7-year-old child made this request.

The CO_2 challenge procedures of Gorman et al[15] were used. Children lay in a sealed plastic canopy ventilated at 40 L/min. Ventilatory parameters are measured without mouthpieces or face masks by assessing changes in airflow from inhalation to exhalation. Children can exit the canopy by lifting a latch. Room-air breathing for 15 minutes was followed by CO_2 inhalation for 15 minutes. Among adults, 5% or 7% CO_2 exposure provokes panic. In the absence of data in children, 3% CO_2 exposure was initially used. This dose was applied to all children younger than 9 years (n=3) and a few older probands (n=3) because there was concern that children might exhibit extreme anxiogenic responses that lasted longer or were more severe than those in adults. Since these types of anxiogenic responses never occurred with 3% CO_2 exposure, 5% CO_2 exposure was used in all others (13 probands and 15 comparisons).

hood[29,30]; (3) evidence of respiratory abnormalities in children with disorders other than panic disorder[8-10]; and (4) the fact that various childhood conditions have been considered precursors of panic disorder.[22-28] Based on findings in adults, we hypothesize that children and adolescents with anxiety disorders exhibit larger minute ventilation, larger tidal volumes, lower end-tidal CO_2, and more variable ventilation during room-air breathing,[1,2,12-21] as well as an enhanced ventilatory response to CO_2 exposure.[15-17]

RESULTS

ASSOCIATIONS WITH AGE

Probands (age, 11.3±2.8 years; age range, 7-16 years) were significantly younger than comparisons (age, 13.5±2.1 years; age range, 9-17 years; t_{31}=2.6; P=.01). When probands younger than 9 years old are excluded, probands (age, 12.2±2.1 years) and comparisons (age, 13.5±2.1 years) do not differ in age (t_{28}=1.8; P=.09). Similarly, there was no age difference (t_{25}=1.0; P>.30) between probands (age, 12.7±2.7 years) and comparisons (age, 13.5±2.1 years) exposed to 5% CO_2.

In probands, age correlated with minute ventilation (Pearson r=0.55; P<.01) and tidal volume (r=0.47; P<.05) during room-air breathing, as well as minute ventilation and tidal volume responses to CO_2 exposure (r=0.50-0.56; P<.01). In comparisons, most of these correlations were in the r=0.15 to 0.40 range; only the correlation between age and minute ventilation response to CO_2 exposure was significant (r=0.57; P=.05).

No statistically significant differences in age-by-physiology correlations were present between probands and comparisons tested by the Fisher r to z transformation (available on request). Since probands are younger than comparisons and since ventilatory measures correlate positively with age, group differences in age might

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ANXIETY RESPONSE

Panic symptoms were rated using the Acute Panic Inventory (API).[10,12,15] Questions on the API were revised and tested to be understandable by children, and the API was reviewed with each child to ensure that questions were understandable. The possibility of a panic attack during CO_2 challenge was discussed at recruitment and on day 1. Children were told that panic attacks involve "sudden increases in fear and breathlessness." Children were told to signal if they wished to stop the procedure. Items on the API were rated by indicating responses on a board. There was 100% agreement for all API items and "panic attack" ratings between 2 raters (D.S.P. and J.M.M.) simultaneously rating 12 children.

A panic attack was defined as the development of crescendo anxiety with fear and at least 4 somatic symptoms, as in the *DSM-III-R*[31] and previous adult studies. This determination was made by an experienced rater of CO_2-induced panic (J.M.M.) who was unaware of clinical status. The rater also identified "near-panic" reactions, defined as crescendo anxiety with fear but insufficient somatic symptoms of panic. The physician observing the procedures (D.S.P.) was not unaware and completed an independent API for only 12 children. The physician and the rater agreed on all dichotomous panic and near-panic ratings.

VENTILATORY PHYSIOLOGY

Tidal volume, minute ventilation, and respiratory rate were measured using spirometery, and end-tidal CO_2 was monitored using capnography.[15] Values were averaged for 30-second epochs. Artifacts were detected using 2 procedures. First, nonphysiological values were removed using preset criteria. Second, raw data and data plots were inspected to ensure that all nonphysiological values had been removed. Data points 2 SDs above the mean for a subject during an epoch were reviewed without knowledge of the clinical status by 3 investigators (D.S.P., J.M.M., and D.F.K.) and were either removed or retained based on consensus. Values were removed when adjacent breaths seemed to be read as 1 breath. For example, a series of 150-mL tidal volume values might be followed by a single 500- to 600-mL value lasting 3 times as long as previous and subsequent 150-mL values. In total, less than 1% of the data contained outliers.

DATA ANALYSIS

Because ventilatory volumes and neural regulation of breathing may correlate with age,[36-39] statistical analyses are conducted for raw data, for age-adjusted data using the entire sample, and for age-adjusted data in subgroups matched for age by excluding probands younger than 9 years. These analyses were also re-run adjusting for height, weight, or various indexes of body size, including body mass index. Results were similar regardless of adjustments; for parsimony, we only present unadjusted and age-adjusted data. Between-group differences in room-air breathing and CO_2 response were examined using independent sample *t* tests and analysis of covariance (ANCOVA).

To test for group differences in breathing regularity,[1,15,19-21] we computed the mean within-subject SD for respiratory parameters during room-air breathing. We rely on SDs across 30-second epochs to provide data in a form comparable with results of our previous studies.[12,13,15] However, analyses of SDs across individual breaths generated identical results (available on request). We applied Mann-Whitney *U* tests since distributions of SDs are unlikely to be normal. As routinely used multivariate nonparametric tests are unavailable, analyses covarying for age were not performed.

Procedures adapted from Gorman et al[15] were used to examine CO_2 response. Using least-squares regression analysis, slope values for each subject were computed for each ventilatory parameter as a function of time. Independent sample *t* tests and ANCOVAs contrast the average slope in the group of probands and comparisons. To parallel the studies of Gorman et al,[15] comparisons were made at 2, 3, 4, and 5 minutes after CO_2 exposure. Slopes were fit using all data for each subject such that an individual's slope at 5 minutes was based on a regression-line fit through all of the data points between time 0 (start of CO_2 exposure) and 5 minutes after CO_2 exposure.

Group differences in panic or near-panic attack rates to CO_2 exposure were tested with uncorrected χ^2 statistics and the Fisher exact test. All statistical tests are 2 tailed, with $\alpha=.05$. All means are presented with SDs.

limit statistical power to test hypotheses. We used Spearman correlations to examine associations between age and respiratory variability due to the nonparametric nature of variability indexes. No correlation was significant in the probands, the comparisons, or the sample as a whole ($r<0.10$ for all).

ROOM-AIR PHYSIOLOGY

Data were unavailable for 1 proband due to a technical malfunction, and one 8-year-old child with separation anxiety disorder refused to enter the canopy. Therefore, room-air data shown in **Table 2** are limited to 18 probands. Probands had significantly larger minute ventilation than comparisons. Although raw differences in tidal volume, respiratory rate, and end-tidal Pco_2 were not significant, between-group differences in tidal volume ($P<.01$) and minute ventilation ($P=.002$) were significant after covarying for age (Table 2).

Differences in room-air physiology were obtained when the sample was restricted to subjects aged 9 years and older. Namely, in analyses covarying for age, probands had significantly larger minute ventilation (5.2±2.7 L/min) than comparisons (3.2±1.6 L/min; $F[1,27]=10.9$; $P<.005$). They also had significantly larger tidal volumes (261±147 mL) than comparisons (166±95 mL; $F[1,27]=4.5$; $P<.05$). Differences in respiratory rate and end-tidal Pco_2 remained nonsignificant.

For measures of respiratory variability in room-air, probands had significantly larger mean SDs in minute ventilation (2.0±2.0 L/min) than comparisons (0.8±0.4 L/min; $z=2.1$; $P<.05$) and significantly larger mean SDs in tidal volume (98±101 mL) than comparisons (39±27 mL; $z=2.1$; $P<.05$). The difference in SD of respiratory rate was marginally significant ($z=1.9$; $P=.06$). Identical results for minute ventilation and tidal volume were found after restricting probands to age 9 years and older. A significant difference in respiratory rate also emerged ($z=2.1$;

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Table 1. Diagnoses in 20 Probands With Anxiety Disorders*

	Proband No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Age, y	8	7	7	10	10	7	10	13	15	11	11	14	11	11	10	16	13	15	13	10
Panic disorder	...	...	...	...	...	...	X	X	X	...	...	...	X	...	...	X	...	X	...	...
Separation anxiety	X	X	X	...	X	X	X	...	...	X	X	X	X	X	...	...	...	...	X	...
Overanxious disorder	...	...	...	...	...	...	X	X	...	X	...	X	...	X	X	...	...	...	...	X
Social phobia	...	...	...	X	...	...	...	...	...	X	...	X	...	X	...	X	X	...	...	...
Major depression	...	...	...	...	...	...	...	...	X	...	...	X	...	...	...	...	...	X	...	...
ADHD*	...	X	X	...	...	...	...	...	X	...	...	...	...	...	...	...	...	...	...	...
ODD/CD	...	...	...	...	...	...	...	...	X	...	...	...	...	...	...	...	...	...	...	...
Received 3% carbon dioxide	†	X	X	X	X	X	X	...	...	...	...	...	...	...	...	...	...	...	...	...
Response to carbon dioxide	†	...	‡	...	...	...	...	...	...	...	...	‡	‡	...	...	...	...	‡	‡	...

**ADHD indicates attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder; CD, conduct disorder; and ellipses, diagnosis or condition not present.*

†*Subject refused to enter the canopy.*

‡*Subject had either a panic attack or a near-panic attack (crescendo anxiety without sufficient other symptoms for a panic attack as categorized by the* Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised).

$P<.05$), with more variability in probands (4.2±2.0 breaths/min) than in comparisons (2.6±0.8 breaths/min).

VENTILATORY RESPONSE TO CO_2

One proband with separation anxiety disorder and 1 healthy comparison asked that the procedures be terminated during room-air breathing. Therefore, CO_2 response data were obtained in 17 probands and 14 comparisons. **Table 3** presents contrast at 4 time points for each group's average slope.

For unadjusted data, probands exhibited a steeper mean respiratory rate slope than comparisons at 4 and 5 minutes. Differences were nonsignificant at 2 and 3 minutes. Differences in minute ventilation and tidal volume responses were nonsignificant at all times. However, adjusting for age, the mean respiratory rate and minute ventilation slopes were significantly steeper in probands than in comparisons at all times. Although these spirometry data were of primary interest, the slope of end-tidal CO_2 through 2 minutes also was significantly steeper (t_{25}=2.3; $P<.05$) in comparisons than in probands (data not shown).

When probands were restricted to children aged 9 years and older, they exhibited steeper slopes in respiratory frequency at all times (2 minutes: $F[1,22]=5.5$, $P<.05$; 3 minutes: $F[1,23]=7.2$, $P=.01$; 4 minutes: $F[1,23]=8.8$, $P<.01$; and 5 minutes: $F[1,22]=5.5$, $P<.05$) in ANCOVAs covarying for age. Probands exhibited a steeper slope in minute ventilation at 4 minutes ($F[1,23]=8.9$; $P<.01$) and 5 minutes ($F[1,22]=5.5$; $P<.05$) after CO_2 exposure. Similarly, after eliminating children who received 3% CO_2, probands exhibited steeper slopes in frequency at all times (2 minutes: $F[1,20]=5.2$, $P<.05$; 3 minutes: $F[1,20]=7.0$, $P<.05$; 4 minutes: $F[1,20]=7.6$, $P=.01$; and 5 minutes: $F[1,18]=6.0$, $P<.05$) in ANCOVAs covarying for age. Probands also exhibited steeper slopes in minute ventilation at 4 minutes ($F[1,20]=7.7$; $P=.01$) and 5 minutes ($F[1,18]=4.8$; $P<.05$) after CO_2 exposure.

PANIC RESPONSES

Most children tolerated challenge procedures well. Neither subject who terminated procedures during room-air breathing had a panic attack. Seven of 18 probands and 3 of 14 comparisons terminated procedures during CO_2 exposure ($\chi^2=1.4$; $P=.24$; $P=.35$ by Fisher exact test). Three probands and no comparisons reported experiencing panic attacks ($\chi^2=2.7$; $P=.09$; $P=.15$ by Fisher exact test). Two other probands but no comparisons had near-panic reactions during CO_2 exposure. Four of 5 panic or near-panic reactions occurred with 5% CO_2 exposure and the fifth with 3% CO_2 exposure. Four of 5 patients with panic or near-panic reactions had separation anxiety, 1 with comorbid panic disorder, while the fifth had panic disorder and a past but not current history of separation anxiety disorder (Table 1). Overall, panic or near-panic responses were more common in probands (5 of 18) than in comparisons (0 of 14) ($\chi^2=4.9$; $P=.03$; $P=.07$ by Fisher exact test). Patients with current separation anxiety disorder (4 of 10) had a higher rate of panic or near-panic responses ($\chi^2=6.7$; $P<.01$; $P<.05$ by Fisher exact test) than comparisons (0 of 14).

COMMENT

COMPARISON WITH DATA IN ADULT PANIC DISORDER

Our first attempt to examine ventilatory physiology in childhood anxiety disorders yielded many findings similar to adult panic disorder. Among the latter, increased variability in respiratory parameters is the best-replicated finding during room-air breathing.[1,2,15,19-21] The present study also found such increased variability. While the mechanisms that account for such increased variability remain unknown, CO_2 perception is likely to play a role, given its effect on respiratory variability.[40-42]

Panic disorder is also associated with room-air hyperventilation.[1-3,12-15,21] Whereas children with anxiety disorders exhibited increased room-air minute ventila-

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Table 2. Mean Ventilatory Indexes During Room-Air Breathing in Probands With Anxiety Disorders and in Psychiatrically Healthy Comparisons

	Minute Ventilation Response, L/min		Tidal Volume, mL		Respiratory Rate, breaths/min		End-Tidal Carbon Dioxide, mm Hg	
	Raw	Age-Adjusted	Raw	Age-Adjusted	Raw	Age-Adjusted	Raw	Age-Adjusted
Probands (n=18)	4.9±2.6	5.2±0.5	246±139	264±27	21.1±4.4	21.1±1.1	37.2±5.8	37.3±1.4
Comparisons (n=15)	3.2±1.6	2.6±0.5	166±95	139±31	20.3±3.0	20.4±1.0	37.5±5.1	37.2±1.5
Statistic*	t_{31}=2.3†	F[1,30]=11.6‡	t_{31}=1.9	F[1,30]=7.4§	t_{31}=0.6	F[1,30]=0.4	t_{31}=0.4	F[1,30]=0.1

*Difference in raw values is tested using an independent sample t test; difference in age-adjusted values is tested using analysis of covariance.
†P<.05.
‡P<.002.
§P<.01.

Table 3. Ventilatory Response* to Carbon Dioxide Challenge

	Intervals Between Carbon Dioxide Exposure							
	2 min		3 min		4 min		5 min	
	Raw	Age-Adjusted	Raw	Age-Adjusted	Raw	Age-Adjusted	Raw	Age-Adjusted
Change in Minute Ventilation, mL/min²								
Probands (n=17)	1245±1854	1657±1734	1691±1978	2137±1933	2195±1918	2701±1692	1844±1459	2233±1692
Comparisons (n=14)	−226±1781	−503±2023	641±2122	−19±2747	1346±1997	553±1843	1411±1471	868±1420
Statistic†	t_{27}=1.5	F[1,26]=8.4‡	t_{27}=1.4	F[1,26]=6.9‡	t_{26}=1.2	F[1,25]=9.2‡	t_{25}=0.8	F[1,24]=5.8§
Change in Tidal Volume, mL/min								
Probands (n=17)	57.9±74.0	58.9±81.1	75.3±71.8	84.2±65.9	77.7±62.8	94.0±53.4	67.9±46.9	82.4±42.2
Comparisons (n=14)	73.0±79.9	71.1±94.6	56.5±67.4	43.3±73.1	77.9±67.4	52.3±58.2	68.3±47.3	49.2±43.8
Statistic†	t_{27}=0.6	F[1,26]=0.1	t_{27}=0.4	F[1,26]=2.1	t_{26}=0.0	F[1,25]=3.5	t_{25}=0.0	F[1,24]=3.6
Change in Respiratory Rate, breaths/min²								
Probands (n=17)	−0.78±3.55	0.04±3.46	0.18±2.28	0.63±2.28	1.04±1.81	1.29±1.86	0.84±1.12	0.99±1.20
Comparisons (n=14)	−2.13±3.82	−3.59±4.04	−0.32±2.42	−1.70±2.53	−1.01±1.89	−1.05±2.03	−0.18±1.08	−0.37±1.24
Statistic†	t_{27}=1.0	F[1,26]=6.0§	t_{27}=1.4	F[1,26]=5.7§	t_{26}=2.4§	F[1,25]=9.0‡	t_{25}=2.5§	F[1,24]=7.8§

*Response is defined as slope of the least-square regression line through all data points between start of carbon dioxide inhalation and last reading in interval (2, 3, 4, or 5 minutes). Slope is fit for each subject in the study. Table shows the contrast of mean slope values in the proband and comparisons.
†Difference in raw value is tested using an independent sample t test; difference in age-adjusted values is tested using an F value from analysis of covariance with age as a covariate; degrees of freedom change as subjects discontinue carbon dioxide inhalation; and degrees of freedom vary across challenges because some children terminated the procedure early and because of missing data.
‡P<.01.
§P<.05.

tion, end-tidal CO_2 did not differ between groups. The lack of a between-group difference in end-tidal CO_2, despite differences in minute ventilation, might result from an overproduction or an inefficient handling of CO_2 in anxious children. Measurement of blood bicarbonate and pH levels are needed to examine these possibilities critically.

The best-replicated physiological CO_2 challenge finding among adults is an enhanced respiratory rate response to CO_2 exposure,[12-17] a pattern also found in the present study. The fact that respiratory rate abnormalities are consistently found across CO_2 challenge studies may suggest a role in anxiety for neural systems controlling respiratory timing. This possibility is supported by research on the neurophysiological basis of dyspnea and CO_2 responsivity.[43-46]

The rate of panic attacks among probands in this study (18%) is considerably lower than that in studies of panic disorder (50%-80%),[1-13] a finding for which there are many explanations. First, the physiological capacity for panic may develop before the mental capacity.[47] While only 18% of probands had panic attacks, probands as a group exhibited many ventilatory features of panic disorder. Second, CO_2 dynamics differ between children and adults, with more complicated peripheral chemoreceptor regulation in children.[36-39] Third, spontaneous panic is rare in this age group.[29] Finally, more than one third of the children with anxiety disorders were exposed to 3% CO_2, which does not provoke panic among adults.

LIMITATIONS

This was our first attempt to apply to children with anxiety disorders the respiratory physiology assessment strategies developed among adults. Limitations in the design raise questions for further research.

Many factors, including age differences across groups and small sample sizes, limit the statistical power of the study. For example, assuming even large effect sizes (Cohen d>0.8), this study had only 50% to 60% power to test hypothesized differences in physiology.[48] Given the correlations between age and physiology, between-

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group age differences place further limitations on power and suggest the need for replication in narrow age ranges. Finally, in interpreting CO_2 response data, comparisons had a steeper slope in end-tidal CO_2 responses than probands, which could result either from the fact that 6 probands were exposed to 3% CO_2 or from the steeper slope in minute ventilation response among probands. In either case, differences in end-tidal CO_2 slopes minimize between-group differences in CO_2 response. In light of these limitations, the results of this study, particularly for nonsignificant comparisons, should be viewed with caution.

It is difficult to untangle the effect of CO_2 as a respiratory panicogen from the stressful nature of a CO_2 challenge. Among adults, psychological factors, including perceptions of control[49,50] and proximity to a "safe" person,[51] may alter responses to respiratory panicogens. One might imagine even greater effects in this regard among children. We reduced such stress by offering encouragement to children and by keeping their parents nearby. Nevertheless, procedure-related psychological stress may contribute to our findings, possibly interacting with the anxiogenic properties of CO_2. Consistent with this possibility, 2 children terminated procedures during room-air breathing, 1 refused to enter the canopy, and 1 had a near-panic reaction that occurred with 3% CO_2 exposure, which does not typically provoke panic in adults (J.M.G., unpublished data, 1996). Future experiments might address this limitation through an experimental control condition in which children breathe room air in the canopy for 30 minutes. As discussed elsewhere,[10,12] such experiments might also contend with order effects and the need to counterbalance the sequence of multiple challenge tests. Alternatively, mouthpiece-based methods for assessing CO_2 response might be considered, although 1 rationale for developing a canopy apparatus was the effect of mouthpieces on ventilation.[15]

In the absence of a psychiatric comparison group, it is unclear whether our findings apply to anxiety disorders or to childhood psychiatric disorders in general. Major depression represents a particularly relevant contrast, given the comorbidity between depression and anxiety, as well as their familial aggregation.[23-27] Among adults, preliminary data suggest that depression in the absence of anxiety is not associated with increased CO_2 sensitivity using either physiological[52,53] or anxiogenic[54] criteria. Conversely, response to respiratory panicogens in depressed adults with panic disorder resembles the response in "pure" panic disorder.[55] In our study, 3 probands had major depression, all with comorbid separation anxiety or panic disorders. Of these, 2 subjects had panic or near-panic reactions to CO_2 exposure, raising questions about the relationship between comorbid anxiety plus depression and respiration. Hence, studies are needed to compare respiratory profiles among children with depression plus anxiety, anxiety only, depression only, and no disorder.

Finally, data on ventilatory physiology in adults derive from studies in patients with panic disorder. The relationship between distinct childhood anxiety disorders and adult panic disorder remains ambiguous.[2,28,29] While our results suggest that children with various anxiety disorders display differences in ventilatory physiology from comparisons, the study was not designed to evaluate the diagnostic specificity of ventilatory abnormalities. To provide the most accurate diagnostic picture, future examinations of this issue should use parallel diagnostic assessment methods in all children and informants, which could not be implemented in our study. Future studies might also examine this issue in adults. There is evidence among adults of some diagnostic specificity for the anxiogenic response to respiratory challenge.[1-3,54,55] However, the diagnostic specificity for abnormalities in ventilatory physiology remains unclear.[4,56]

Our study provides directions for future research on respiratory correlates of individual childhood anxiety disorders, as there was some evidence of associations among separation anxiety disorder, panic disorder, and CO_2-induced panic. Four of 5 patients experiencing panic or near-panic CO_2 responses had current separation anxiety disorder; the fifth had remitted separation anxiety disorder. Two of 6 patients with panic disorder had panic or near-panic reactions. These results are consistent with theories that suggest a developmental progression from childhood separation anxiety disorder to adolescent or adulthood panic disorder.[2,22,24-26] Probands with separation anxiety disorder without panic disorder (age, 9.9±2.6 years) were significantly younger (t_{14}=2.6; $P<.05$) than probands with panic disorder (age, 13.3±2.4 years), consistent with developmental perspectives. Future research on this issue might examine developmental relationships among separation anxiety disorder, CO_2-induced panic, and future panic disorder or familial relationships among panic disorder, separation anxiety disorder, and CO_2-induced panic.

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Corresponding author: Daniel S. Pine MD, New York State Psychiatric Institute, PO Box 78, 722 W 168th St, New York, NY 10032.

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