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CO_2 Challenge Reactivity as a Prospective Predictor of Panic Attacks

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Abstract

CO_2-induced fear responding was prospectively evaluated as a risk factor for the development of anxiety pathology in a nonclinical sample (*N* = 404) followed for two years. Baseline response to a CO^2 challenge was a very strong predictor of future panic attacks (though not for panic disorder or other anxiety disorders).

Keywords

carbon dioxide; panic attack; longitudinal

1. Introduction

CO_2 challenge has been extensively utilized to explore the nature of panic and panic disorder. The current study addresses one of the main limitations of literature exploring CO_2-reactivity as a risk factor for panic-related pathology. The primary question of interest is whether CO_2-induced reactivity is predictive of the later development of panic attacks, panic disorder, or other anxiety disorder diagnoses. Studies have shown that patients with panic disorder exhibit increased rates of panic and fear responding to CO_2 inhalation (Papp et al., 2003), suggesting that CO_2 hypersensitivity may be a risk marker for the development of panic disorder. However, such studies have relied on cross-sectional designs and therefore leave unanswered the question of whether CO_2 reactivity truly serves as a risk factor for panic-related symptoms and diagnoses, or whether it is merely concomitant to the experience of panic symptoms. The current research thus used a prospective design to redress this limitation.

A second, related aim of the current research pertains to the link between family history of anxiety and CO_2 reactivity. We evaluated 1) whether a family history of anxiety is associated with CO_2-induced reactivity and 2) whether family history of anxiety might modulate the influence of CO_2-induced reactivity on the later development of anxiety pathology. Previous literature provides mixed support for the link between family history of anxiety and CO_2 reactivity. Exaggerated CO_2 –induced fear reactivity has been found in unaffected, first degree relatives of patients with panic disorder (Coryell et al., 2001;Perna, Cocchi, Bertani, Arancio, and Bellodi, 1995;Perna, Ieva, Caldirola, Bertani, and Bellodi, 2002), suggesting that CO_2 reactivity is a familial marker for the development of panic pathology. Such studies, however,

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have focused largely on healthy, adult relatives who have presumably passed through the highest risk period for panic disorder. Therefore, evidence for CO_2 reactivity as a premorbid, familial risk factor is limited. Indeed, a recent report evaluated healthy children and adolescents using a 5% CO_2 challenge (Pine et al., 2005). This study observed no link between offspring of patients with panic disorder or other anxiety disorders and enhanced fear responding to the CO_2 challenge.

2. Method

2.1 Assessments

2.1.1 Diagnostic Interview—Psychiatric diagnoses were made using structured diagnostic interviews (SCID-NP; 8). Interviews were conducted by research assistants with extensive training in SCID administration and scoring.

2.1.2 Assessment of Family History of Anxiety—A semi-structured interview was used to ascertain lifetime history of significant anxiety problems in first-degree relatives of the participants. This method is widely used and has been found to be reliable and valid for most Axis I conditions, including anxiety disorders (Nardi et al., 2005;Zvolensky and Raulin, 1999). The interview was developed for this study based on similar research. Participants are essentially asked whether their mother, father and siblings had ever either been hospitalized or treated for an anxiety problem. Positive responses were queried to obtain more detailed information though no specific diagnoses were assigned. Lifetime hospitalization or treatment for an anxiety problem was endorsed for one first-degree relative in 22.7% (n = 86) of the sample (an additional 4.0% (n = 15) endorsed anxiety treatment in 2 first-degree relatives). For analytic purposes, this variable was collapsed indicating either a positive or negative family history of anxiety problems.

2.1.3 Acute Panic Inventory (API)—The API has been commonly used in prior studies evaluating panic provocation as well as those investigating familial CO_2 hypersensitivity. Participants rate the severity of each symptom from 0 (absent) to 3 (severe). The API also includes a Subjective Units of Distress (SUDS) rating of self-reported anxiety (0 - No Anxiety, 100 - Extreme Anxiety). In the present report, API reactivity indices (pre-post CO_2 challenge in API total symptoms and API-SUDS) were the primary predictors of interest.

2.1.4 20% CO_2 Challenge—Participants underwent a 20-s gas inhalation (20% CO_2, 80% O_2) administered through a continuous positive air pressure Downs C-Pap Mask with nose clip and head strap to assess CO_2 reactivity. The 20% CO_2 challenge has been increasingly used in the recent years, with well over 20 empirical studies now on this topic (Lejuez, Eifert, Zvolensky, and Richards, 2000). Work using 20% CO_2 suggests it is a powerful panicogenic agent that can be administered repeatedly, for various durations of time (see Zvolensky and Eifert, 2000, for a review).

2.2 Procedure

Individuals were recruited from the Columbus, OH metropolitan area school system (n = 46), the Ohio State University (n = 263), and the Columbus, OH community (n = 96). Eligibility criteria included age (range = 15-30), scoring > 1.5 standard deviations above the mean on the Anxiety Sensitivity Index for a nonclinical community sample (Schmidt and Joiner, 2002), and no current or recent psychiatric history (no diagnoses in the past 12 months and no current Axis I diagnosis). This young adult sample (age M = 19.3, SD = 3.9; Female = 61%) was followed for approximately 24 months (see (Schmidt et al., in press) for more details). Participants initially completed the SCID and, if eligible, completed a CO_2 challenge. Participants completed an API following a 5-minute adaptation period. After approximately 3

minutes, participants received a 20-s inhalation of CO_2-enriched air. Immediately following the inhalation, participants returned to breathing normal room air and completed another API. Participants were followed for up to 24-months (average = 18 months). During the follow-up evaluations, the SCID was readministered to assess for the occurrence of spontaneous panic attacks and Axis I disorders during the follow-up interval.

3. Results

3.1 20% CO_2 Challenge Reactivity

Evaluation of pre-post changes in API using repeated measures ANCOVA indicated that, after controlling for condition, exposure to the CO_2 challenge resulted in significant increases in API Symptoms (F (1, 402) = 36.4, $P < 0.001$, partial $\eta_2 = 0.08$) and SUDS (F = (1, 402) = 45.9, $P < 0.001$, partial $\eta_2 = 0.10$) relative to baseline. Evaluation of those reporting significant fearful responding to the challenge (SUDS > 50) indicated 25/404 (6.2%) showed SUDS levels in the range of 60-80 with 80 being the maximum score. Thus, in this sample, approximately 5% showed substantial sensitivity to the CO_2 challenge. Consistent with Pine et al. (2005), family history of anxiety was not significantly associated with API-symptom reactivity (r (df = 402) = 0.06, $P > 0.10$) or SUDS reactivity (r (df = 402) = -0.04, $P > 0.10$).

3.2 Zero-order Correlations among Variables

Table 1 displays zero-order correlations for the main predictor and outcome variables. The pattern of associations indicates family history of anxiety was not significantly associated with the incidence of anxiety pathology. However, CO_2 reactivity (both API and SUDS) showed very strong associations with later panic attacks. In fact, every individual reporting a panic attack during follow-up showed initial CO_2-induced sensitivity (SUDS >50). CO_2 reactivity indices were not associated with new diagnoses.

3.3 Prediction of the Incidence of Panic Attacks and Diagnoses during the Follow-up Period

Follow-up data were obtained for 73% of the sample (n = 295). During the follow-up period, there was a total incidence of 6.4% (n = 19) for anxiety disorder diagnoses (diagnoses included social anxiety disorder (n = 6), panic disorder (n = 5), generalized anxiety disorder (n = 2), specific phobia (n = 2) and anxiety NOS (n = 4). The incidence of panic attacks during follow-up was 8.1% (n = 24). To provide an accurate prospective assessment of the incidence of new diagnoses and panic attacks during the follow-up period, analyses evaluating incidence excluded those presenting at baseline with a lifetime history of any anxiety disorder or panic attacks at baseline.

A series of stepwise logistic regression analyses were used to predict diagnostic outcomes. In the first step, experimental condition and gender were entered to statistically control for these variables. In the second step, the CO_2 reactivity score (API or SUDS) and family history were entered. Finally, a CO_2 reactivity x Family History variable was entered in the final step to ascertain whether the risk factors interacted to predict outcomes.

Even after controlling for condition and gender, CO_2 SUDS reactivity was highly associated with incidence of spontaneous panic attacks during follow-up (β (1) = 0.14, SE = 0.67 $Wald$ = 33.90, $P < 0.001$). Similarly, CO_2 API symptom reactivity was a unique predictor of panic attacks (β(1) = 0.20, SE = 0.04 $Wald$ = 31.60, $P < 0.001$). Notably, there were no significant main effects for family history and no significant interaction between family history and CO_2 reactivity. Family history, CO_2-reactivity, and their interaction were not significantly associated with anxiety diagnoses.

4. Discussion

CO_2 reactivity was not associated with later panic disorder or other anxiety diagnoses. This is the first report to provide prospective evidence that CO_2-induced reactivity is a risk factor for the later development of panic attacks, suggesting that this may be a specific marker for panic attacks rather than clinical syndromes, though the follow-up duration in this study was limited. The association between CO_2-induced reactivity and subsequent panic appears to be quite substantial since *every* panic attack reported during follow-up occurred among the small percentage of participants showing substantial fear in response to the challenge. Consistent with recent reports (Pine et al., 2005), family history of anxiety was not associated with CO_2-induced symptoms or fear. Nor did family history predict any anxiety outcomes. The current study suggests CO_2-induced reactivity is a potent marker for the development of panic pathology.

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Table 1

Zero-order Correlations for Main Study Variables.

	Panic Attacks	Panic Disorder	Any Anxiety Dx
1. Family History of Anxiety	0.00	0.10	−0.01
2. CO_2 Reactivity - SUDS	0.55*	0.03	0.11
3. CO_2 Reactivity – API	0.47*	−0.01	0.00

n range = 241-379.

*Note. Correlation is significant at the 0.001 level (2-tailed); 1 – Family History of Anxiety – Any anxiety problems endorsed in first degree relatives; 2 – SUDS – Change in Anxiety in Response during the CO_2 Challenge; 3 – API – Change in API Symptoms in Response during the CO_2 Challenge; Panic Attacks – Spontaneous Panic Attacks during Follow-up; Panic Disorder – Panic Disorder Diagnoses during Follow-up; Any Anxiety Dx – Any Anxiety Disorder Diagnosis during Follow-up.