Prospective Evaluation of Panic Potentiation Following 35% CO_2 Challenge in Nonclinical Subjects

Patrick J. Harrington, Norman B. Schmidt, Ph.D., and Michael J. Telch, Ph.D.

Objective: *The authors examined the effect of panic provocation on the subsequent development of panic attacks and panic disorder in nonclinical subjects with no history of spontaneous panic.* *Method:* *Sixty-two subjects who had completed a study examining fearful responses to a single vital capacity inhalation of 35% CO_2 were reevaluated 1 year following the challenge test.* *Results:* *Challenge-induced panic was not related to the later development of panic or panic disorder. According to the Structured Clinical Interview for DSM-III-R—Non-Patient Edition, none of the subjects met DSM-III-R criteria for panic disorder and only six subjects reported spontaneous panic during the year after panic provocation. Of the six subjects who experienced spontaneous panic, two had panicked in response to the CO_2 challenge.* *Conclusions:* *The experimental provocation of panic in nonclinical subjects appears to be a safe research paradigm for exploring the psychopathogenicity of panic disorder.*
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The experimental induction of panic through biological challenge is a widely used research paradigm for investigating the pathogenesis of panic. The use of challenge tasks has greatly expanded during the past decade, as evidenced by the growing number of challenge agents that are being used to investigate suspected biological vulnerabilities. These agents include sodium lactate (1), yohimbine (2), CO_2 (3), caffeine (4), and cholecystokinin (5). In addition, proponents of cognitive theories of panic have increased their use of biological challenges to investigate psychological factors implicated in the psychopathogenicity of panic disorder (6, 7).

Nonclinical subjects play two important roles in biological challenge studies. They are used as control subjects for comparative purposes (8), and those with no previous history of panic attacks allow researchers to explore the role of suspected vulnerability factors without the threat that the suspected vulnerability is merely a concomitant or consequence of panic. Several challenge studies have relied solely on nonclinical subjects to examine purported psychological vulnerabilities that may influence panic (9, 10; our unpublished work), and it is likely that the use of nonclinical subjects will increase. Therefore, it is important to document, in particular for institutional review boards, that laboratory-induced panic will not potentiate panic disorder in individuals with no previous history of panic. Evaluation of panic potentiation is particularly important in view of the fact that several investigators have reported substantial levels of panic in nonclinical subjects undergoing biological challenge (5, 11; our unpublished work).

In the current prospective study we investigated the long-term effects of a 35% CO_2 challenge in nonclinical subjects who had no history of naturally occurring panic. We were particularly interested in assessing the effects of CO_2-provoked panic on the later development of panic attacks or panic disorder. We expected that the experience of panic in response to CO_2 challenge would not create a greater risk for the later development of panic. However, we hypothesized that subjects who were identified as having high scores on the psychological vulnerability factor described as anxiety sensitivity (i.e., the fear of body sensations) would be at greater risk for the development of panic and panic disorder.

METHOD

Sixty-two (78%) of 79 subjects who had completed a single vital capacity 35% CO_2 challenge experiment were reevaluated 1 year following the challenge test. There were no significant differences between the subjects who were successfully contacted and those who were lost to follow-up in demographics, symptom measures, or subjective and physiological response to the CO_2 challenge (all p values >0.05, chi-square tests for categorical variables and t tests for con-

Received Sept. 15, 1995; revision received Jan. 18, 1996; accepted Feb. 22, 1996. From the University of Texas at Austin and the Uniformed Services University of the Health Sciences, Bethesda, Md. Address reprint requests to Dr. Telch, Department of Psychology, Mezes 330, University of Texas at Austin, Austin, TX 78712.

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tinuous variables). Subjects included 35 men and 27 women between the ages of 18 and 29 who were originally selected for the challenge study on the basis of anxiety sensitivity scores one standard deviation above or below the mean for a nonclinical population. Subjects in the high anxiety sensitivity group did not differ on demographics from those in the low anxiety sensitivity group, but they did score higher on self-report measures of state and trait anxiety and depression. Exclusion criteria included 1) history of an unexpected panic attack or panic disorder, 2) medical conditions contraindicating CO_2 inhalation (e.g., renal disease or heart disease), and 3) current use of psychotropic medications.

Subjects participating in a previous study examining the role of anxiety sensitivity in a 35% CO_2 challenge (our unpublished work) were contacted 12 months after the challenge. After providing written informed consent, subjects were given the panic disorder section of the Structured Clinical Interview for DSM-III-R—Non-Patient Edition (12). The subjects' 12-month history and current status of panic disorder diagnostic criteria were assessed.

RESULTS

Six (9.7%) of 62 subjects reported an unexpected panic attack during the 12-month follow-up period. One subject experienced two panic attacks (4 months apart), and five subjects reported only one each. The average occurrence of panic was 6 months following the CO_2 challenge; the most proximal panic attack took place 4 months following the challenge. None of those experiencing a panic attack reported significant distress or worry associated with their attacks. In addition, none of the subjects met DSM-III-R criteria for panic disorder or any other anxiety disorder during the follow-up period.

Logistic regression analyses indicated that panic status (yes or no) during CO_2 inhalation did not significantly predict panic attack frequency (yes or no) at follow-up (χ^2=0.55, df=1, N=62, p>0.46, odds ratio=2.05, 95% confidence interval=0.33–12.64). Two of the 13 subjects who had panicked during the challenge, compared with four of the 49 subjects who did not panic, reported a panic attack during the follow-up period.

Although anxiety sensitivity status (high or low) predicted panic during the original experiment, it did not significantly predict the development of panic during the follow-up period (χ^2=0.62, df=1, N=62, p>0.43, odds ratio=2.0, 95% confidence interval=0.39–11.82). Of the six subjects who panicked over the past year, four (12.5%) were originally in the high anxiety sensitivity group (N=32), and two (6.7%) were in the low anxiety sensitivity group (N=30). The combination of high anxiety sensitivity and panic during the challenge was not associated with a greater likelihood of panic during follow-up (χ^2=0.37, df=1, N=62, p>0.85, odds ratio=0.82, 95% confidence interval=0.23–4.41). One subject in each of the two anxiety sensitivity groups panicked both during the challenge and in the follow-up period.

DISCUSSION

Findings from the present study indicate that panic induced by 35% CO_2 inhalation is a safe procedure with minimal long-term risk for the development of anxiety pathology. None of the challenged subjects met diagnostic criteria for panic disorder during the follow-up period, and only a small percentage reported experiencing a panic attack. On average, the occurrence of spontaneous panic was not proximal to the challenge but took place 6 months after the challenge, indicating no clear temporal relationship. In addition, the overall percentage of subjects reporting panic is lower than, or comparable to, panic frequency data reported in nonclinical samples (13).

Consistent with our prediction, the provocation of a panic attack in nonclinical subjects with no previous history of panic did not predict the subsequent development of panic attacks or panic disorder. Therefore, initial fearful responding to the challenge agent does not appear to place nonclinical subjects at risk for later development of panic. Twice as many subjects with high anxiety sensitivity scores as subjects with low anxiety sensitivity scores reported an unexpected panic at follow-up. However, this difference was not statistically significant, indicating no clear interaction between this psychological vulnerability factor and the experience of challenge-induced panic or the ensuing development of panic symptoms.

In sum, panic induced by 35% CO_2 challenge does not adversely prime or potentiate panic disorder in nonclinical subjects and appears to offer a safe research paradigm for unraveling the psychopathogenicity of panic disorder. Adequate debriefing may play a role in helping to prevent potentiation (e.g., debriefing may inoculate against future panic by normalizing anxiety sensitivity), but this requires further evaluation. We would caution that this study does not rule out the possibility that panic provocation agents other than CO_2 may potentiate subsequent panic in nonclinical subjects. One follow-up study found that nonclinical subjects were not at greater risk for future panic attacks after challenge with lactate or isoproterenol (14). We recommend that similar follow-up evaluations be conducted for other challenge agents.

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