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Anxiety sensitivity and 35% CO_2 reactivity in patients with panic disorder

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Abstract

Objective: The present study examines the possible relationships between anxiety sensitivity (AS) and reactivity to the 35% carbon dioxide (CO_2) challenge in panic disorder (PD). **Methods:** One-hundred eight patients with PD underwent the 35% CO_2 challenge and completed the Anxiety Sensitivity Index (ASI). Multiple regression analyses were applied to evaluate the role of AS as a predictor of CO_2-induced anxiety. **Results**: Fifty-six patients with PD showed high AS scores, whereas 48 showed medium scores and 4 low scores. ASI scores significantly predicted symptomatological reaction to CO_2 but not subjective induced anxiety. **Conclusion:** These findings suggest that the fear of anxiety-related bodily sensations was related to the symptomatological reactivity to CO_2 but did not seem to play a crucial role in the modulation of the subjective anxiogenic/panicogenic response to hypercapnia in patients with PD.

Keywords: Anxiety sensitivity; Carbon dioxide; Cognitive; Panic disorder

Introduction

Panic-provoking procedures provide closed systems capable of elucidating panic disease mechanisms [1], and one of the most thoroughly investigated experimental procedures used to induce anxiety and panic is the inhalation of hypercapnic gas mixtures [2]. Single or double breath inhalations of 35% carbon dioxide (CO_2) have been reported to induce anxiety and panic in patients with panic disorder (PD) [3–7], but the degree of anxiety reactivity reported is not homogeneous. Almost 50% of patients with PD shows a very strong reaction to CO_2 similar to, or even worse than, the feelings experienced during spontaneous panic attacks [6], while others, around 20–25%, have little or no reaction [8]. The reasons for this heterogeneity have not yet been fully investigated. We have recently [8] reported an association between 35% CO_2 sensitivity and familial vulnerability to PD. Patients with positive responses to 35% CO_2 showed a higher morbidity risk than patients with negative responses. Yet this factor alone was not adequate to fully explain the heterogeneity of CO_2 responses in patients with PD. Among the factors that could explain this heterogeneity, anxiety sensitivity (AS) may play a significant role [9]. AS reflects the fear of anxiety-related bodily sensations that arises from cognitive misinterpretation leading to the belief that these symptoms might have harmful consequences. For example, subjects with high AS may believe that rapid heartbeats signify an impending heart attack, whereas subjects with low AS will merely regard them simply as unpleasant [9]. Many studies have reported that AS is a dispositional construct conceptually distinct from trait anxiety [10–13] and is not interchangeable with measures of general anxiety like the State–Trait Anxiety Inventory (STAI) for trait anxiety [13,14]. Although PD may exacerbate AS, nonclinical subjects who have never experienced panic attacks show relevant beliefs about the harmfulness of anxiety symptoms. High AS might develop in ways other than subjective experiences with panic attacks, e.g., through misinformation about heart disease or after watching someone die of a heart attack [9,15–17]. High AS might constitute a cognitive risk factor for the development of PD [9,18,19] and might be a predictor of the

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anxious response to panic-provoking challenges [9,20]. Few studies have investigated the relationships between CO_2 challenges and AS, and the results are contrasting. Koszycki and Bradwejn [21] reported that there was no correlation between AS and most of the dimensions of behavioral reactivity to 35% CO_2. Rapee et al. [22] reported that AS was the only significant predictor of 5.5% CO_2-induced fear in patients with anxiety disorders. Telch and Harrington [23] reported that subjects with high AS who had never experienced panic attacks exhibited rates of 35% CO_2-induced panic, which were comparable to those of patients with PD. AS has been reported to be an element that can be used to predict the response to CO_2 challenges in healthy subjects [24,25], as well as in a mixed sample of controls and patients with PD [26]. Finally, AS has been reported to be associated with the tendency to panic in response to voluntary hyperventilation [14,27,28]. The main aim of the present study was to investigate the possible relationships between AS and the responses to 35% CO_2 inhalations in patients with PD.

Method

One hundred eight patients with PD with/without agoraphobia with no concurrent medical problems and no Axis I diagnoses other than PD, except specific phobia, were included in this study (74 women and 34 men, mean age 31.3 ± 10.8 years). Patients were consecutively recruited over 18 months at San Raffaele Hospital in Milan, Italy. Eighty-five patients (79%) admitted to this study were agoraphobics. Diagnoses were made by a senior psychiatrist using the Schedule for Affective Disorders and Schizophrenia, Lifetime Version (SADS-LA-IV), modified for the Study of Anxiety Disorders [29]. Criteria for exclusion were those related to the 35% CO_2 challenge [6]. At the time of the challenge, subjects were not to have taken any medication for at least 2 weeks. The proportion of patients who took drugs for a lifetime was 70 (65%): 30 took benzodiazepines alone, 10 tricyclics alone, 20 a combination of benzodiazepines and tricyclics, 3 reversible inhibitors of monoamine oxidase, 7 SSRI, and no one was treated with fluoxetine. Patients had also been asked to refrain from alcohol for at least 36 h, xanthines for at least 8 h, and food or smoking for at least 2 h before the test. After a complete description of the study to the participants, informed consent was obtained. Subjects were tested in a double-blind random design, described in detail elsewhere [6]. Briefly, subjects were informed that they would be inhaling two harmless gas mixtures containing different percentages of CO_2 and O_2, and that they might experience some discomfort, ranging from a few neurovegetative symptoms to a definite sensation of anxiety/discomfort with several somatic and/or cognitive sensations. The word "panic attack" was never mentioned. Vital capacity was measured, and then each subject inhaled one vital capacity of 35% CO_2 and 65% O_2 or compressed air in a randomly assigned order. There was an interval of 25–30 min between the two inhalations. The responses to the challenges were evaluated by a Visual Analogue Scale for Anxiety (VAS-A) and by the Panic Symptom List (PSL) [30]. The VAS-A describes the degree of global subjective anxiety on a continuum from 0 (*no anxiety present*) to 100 (*the worst anxiety ever imaginable*), and the PSL is a self-administered questionnaire assessing each of the DSM III-R/IV 13 symptoms of PD on a five-point scale ranging from 0 (*absent*) to 4 (*very intense*) (range 0–52). From the PSL, the following indicators were obtained: the Total Symptom Score (TSS = sum of all the 13 panic symptoms), the Somatic Symptom Score (SSS = TSS scores from depersonalization/derealization, fear of dying, and fear of losing control or going crazy items), and the Cognitive Symptom Score (CSS = score from fear of dying item + score from fear of losing control or going crazy item). The symptomatological reaction to CO_2 was assessed by the Δ scores (scores after CO_2 scores before CO_2). In order to check the baseline influences on quantitative assessments of 35% CO_2-induced anxiety, the global anxiety reactivity was evaluated as Δ%VAS-A (the percentage of maximum increment or decrement possible on the VAS-A scale) [8] and calculated as follows: (a) if VAS-A (post-CO_2 VAS-A values − pre-CO_2 VAS-A values) was positive, then $\Delta\%\text{VAS-A} = \text{VAS-A} \times 100/(100 - \text{VAS-A}$ before $CO_2)$; (b) if VAS-A was negative, then $\Delta\%\text{VAS-A} = \text{VAS-A} \times 100/\text{VAS-A}$ before CO_2. According to the scales described and DSM IV criteria, which define a panic attack, the reaction to the 35% CO_2 challenge was considered to be an induced panic attack when there was included a sensation of fear or panic with at least $\Delta\%\text{VAS-A} \geq 26$, an ideal threshold previously shown by a receiver operating characteristic (ROC) analysis of the 35% CO_2 challenge to separate panic patients and healthy controls with a positive predictive power of 91% and a negative predictive power of 75% [30], and an increase of the scores of at least four symptoms on the PSL. Before the 35% CO_2 challenge, each patient completed the STAI, state version [32], and the Anxiety Sensitivity Index (ASI) [33–35]; ASI is a 16-item self-administered scale developed to measure the fear of anxiety sensations; respondents indicate their degree of endorsement for each item on a five-point scale that ranges from 0 (*very little*) to 4 (*very much*). The mean normal score of ASI is 18.4 ± 8.5 and, according to the score's distribution, subjects were classified into three groups with a high (ASI score 27), a medium ($10 \leq$ ASI score 26), and a low (ASI score 9) AS [34]. To assess the significance of differences in continuously distributed variables, Student's *t* test was performed, while for dichotomous variables, chi-square analyses were applied. Standard multiple regression analyses were applied to evaluate the role of anticipatory anxiety (VAS-A before CO_2), state anxiety (STAI), and AS (ASI) as predictors of CO_2 reactivity expressed both as VAS-A after CO_2 and Δ%VAS-A. Similarly, multiple regression analyses were applied to evaluate the role of