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Hypoventilation Therapy Alleviates Panic by Repeated Induction of Dyspnea

Alicia E. Meuret, Thomas Ritz, Frank H. Wilhelm, Walton T. Roth, and David Rosenfield

ABSTRACT

BACKGROUND: Previous research has shown that hypoventilation therapy reduces panic symptoms in part by increasing basal partial pressure of carbon dioxide (PCO_2) levels. We tested an additional pathway by which hypoventilation therapy could exert its therapeutic effects: through repeated interoceptive exposure to sensations of dyspnea.

METHODS: A total of 35 patients with panic disorder were trained to perform exercises to raise their end-tidal PCO_2 levels using a portable capnometry device. Anxiety, dyspnea, end-tidal PCO_2, and respiratory rate were assessed during each exercise across 4 weeks of training. Mixed-model analysis examined whether within-exercise levels of dyspnea were predictive of reduction of panicogenic cognitions.

RESULTS: As expected, within-exercise anxiety and respiratory rate decreased over time. Unexpectedly, PCO_2 dropped significantly from the beginning to the end of exercise, with these drops becoming progressively smaller across weeks. Dyspnea increased and remained consistently above basal levels across weeks. As hypothesized, greater dyspnea was related to significantly lower panicogenic cognitions over time even after controlling for anxiety and PCO_2. Additional exploratory analyses showed that within-exercise increases in dyspnea were related to within-exercise increases in anxiety but were not related to within-exercise increases in PCO_2.

CONCLUSIONS: In support of the interoceptive exposure model, we found that greater dyspnea during hypoventilation exercises resulted in lower panicogenic cognitions even after the effect of PCO_2 was taken into account. The findings offer an additional important target in panic treatment.

Keywords: Dyspnea, Exposure, Interoception, Panic, Respiration, Therapy

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Panic disorder (PD) is unique among the anxiety disorders in that its reported symptoms are primarily of a physical nature (1). Attacks are discrete periods of intense uncontrollable fear, the symptoms of which can be roughly divided as originating from one of three systems: the autonomic nervous system (e.g., pounding heart, sweating), the respiratory system (e.g., shortness of breath, chest tightness), and a cognitive system (e.g., depersonalization, fear of losing control, fear of dying). Among these symptoms, heart palpitations, dizziness, and dyspnea (shortness of breath) are rated as the most severe during the attacks themselves (2). The strikingly physical nature of the symptoms has led to decades of research on the possible biological causes of PD. One prominent theory is the suffocation false alarm theory (3), which postulates a causal relationship between a faulty respiratory control system and panic. Specifically, hypersensitive medullary chemoreceptors result in a lower set point for a suffocation alarm. Triggering that alarm, by means of even small rises in partial pressure in carbon dioxide (PCO_2), leads to compensatory hyperventilation, a state in which rate and depth of breathing exceeds metabolic demands, which in turn leads to dyspnea (air hunger, shortness of breath, and feelings of suffocation) and a cascade of succeeding panic symptoms. In this context, chronic hyperventilation is an adaptation to a lowered suffocation alarm threshold, keeping PCO_2 low enough to avoid triggering the alarm. However, hyperventilation itself can also create symptoms typical for panic: air hunger, dizziness, tingling sensations, chest tightness, shortness of breath, and heart palpitations. Support for the notion of heightened chemosensitivity comes from animal research demonstrating chemosensitivity of cells in the amygdala (4) that, with increased PCO_2, triggers intense fear responses. Support also comes from human research on breath holding (5,6), CO_2 inhalation challenges (7,8), basal PCO_2 levels (9,10), and PCO_2 rises before out-of-the-blue panic attacks (11) in individuals with high suffocation fears or panic. However, interoceptive sensory (e.g., cardiac) or nonsensory (e.g., cognitive) pathways, other than chemosensory ones, can also elicit panic, as demonstrated in an isoproterenol paradigm in twins with bilateral amygdala lesions (12).

To test whether normalization of hypocapnia (defined as low arterial PCO_2) would lead to reduction of panic symptom severity, we devised an intervention to systematically increase basal PCO_2 into a normocapnic range (hypoventilation therapy). We speculated that by increasing basal PCO_2, patients

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with PD would have less risk of hyperventilation-induced panic and would exhibit a desensitization of a hypersensitive suffocation alarm system. To achieve this goal, patients received a portable capnometer with breath-by-breath feedback and storage of their end-tidal carbon dioxide (along with respiratory rate). Patients were instructed to follow audio-guided exercises twice daily for 4 weeks, with the goal of increasing PCO_2 through slower, shallower breathing (i.e., less tidal volume). Findings from three randomized controlled studies (13–15) showed that this hypoventilation therapy resulted in sustained increases in PCO_2 and significant reductions in panic symptom severity. Importantly, rises in PCO_2 mediated reductions of panicogenic cognitions and improvements of perceived control (14,16). By contrast, changes in respiratory rate were unrelated to therapeutic improvements and, notably, respiratory rate was not related to PCO_2. Similar improvements were found in patients who had PCO_2 increases during psychological treatments that neither targeted PCO_2 nor offered PCO_2 feedback [cognitive therapy (14)] or treatments that targeted hypocapnia in asthma but not panic/anxiety symptoms (17). These findings argue against simple demand characteristics or expectations' being responsible for the observed improvements.

Another mechanism through which hypoventilation therapy could exert its therapeutic effects is repeated exposure to sensations of dyspnea, which in turn could lead to desensitization of the central fear network (18). Dyspnea is a complex sensation (19), and various aspects of hypoventilation therapy could cause dyspnea. Dyspnea could be caused by either high or low PCO_2 levels during the exercises because both can cause shortness of breath or suffocation symptoms. In addition, the strong voluntary control over breathing required by the exercises recruits respiratory muscles, which are known to induce dyspnea sensations independent from respiratory gas exchange (20). In line with possible mechanisms in interoceptive exposure (21), prolonged and repeated exposure to dyspnea triggered by the breathing exercises could lead to reduction of panicogenic cognitions through desensitization of the central fear network. This additional pathway would be supported if dyspnea increased during breathing exercises (hypothesis 1) and if greater within-exercise exposure to dyspnea was related to subsequently fewer panicogenic cognitions over and above within-exercise PCO_2 changes (hypothesis 2). This study is the first to assess the impact of within-exercise changes in dyspnea and PCO_2 as alternative targets to improvement in panic pathology. Prior interoceptive exposure studies have studied the effects of only longer-term changes (i.e., pretreatment to posttreatment) of PCO_2 and dyspnea in interoceptive exposure (15,22).

METHODS AND MATERIALS

Sample

The sample comprised 35 patients (22 women and 13 men) with a principal DSM-IV diagnosis of PD with (n = 19) or without (n = 16) agoraphobia (23). The current article reports unpublished data from a randomized controlled trial testing the efficacy of capnometry-assisted respiratory training (13). Inclusion criteria were as follows: 1) age 18 to 60 years; 2) if on psychotropic medications, on stable doses for at least 3 months prior to the study with an agreement not to change dosage until after the 2-month follow-up; 3) no evidence of any organic mental disorder, suicidality, schizophrenia, alcohol or drug dependence, cardiovascular disease, pulmonary disease, epilepsy, or pregnancy; and 4) no additional psychological treatment until after the 2-month follow-up. The mean age was 41 years (SD = 8.6, range = 23–54). The majority of the sample was married (n = 20), employed (n = 26), and well educated (mean = 17 years, range = 12–25). Race/ethnicities included white (n = 30), Hispanic (n = 1), African American (n = 1), and Asian (n = 3). PD duration averaged 8 years (range = 0.5–32). Agoraphobic avoidance was assessed by item 4 of the Panic Disorder Severity Scale (24) and was reported by 82.9% of participants, with 31.4% classified as mild, 31.4% moderate, 11.4% severe, and 8.6% extreme. In total, 17 participants had at least one secondary current DSM-IV Axis I diagnosis; of these, 13 had another anxiety disorder and 4 had both an anxiety disorder and a mood disorder. Diagnosis was assessed using the Structured Clinical Interview for DSM-IV–Patient Edition (25). Interrater reliability was high for PD and other Axis I diagnoses (κ = 1.00 and κ = 0.83, respectively). In total, 11 patients were on a stable dose of psychotropic medications: benzodiazepines (n = 6), antidepressants (n = 3), beta blockers (n = 1), and other anxiolytics (n = 1). Basal pretreatment PCO_2 was 32.3 mmHg (SD = 4.57, range = 20.6–39.0), with 68.6% falling into the hypocapnic range [$PCO_2 < 35$ mmHg (26)]. The mean resting respiratory rate was 12.4 breaths per minute (SD = 4.37, range = 4.3–24.6).

The study was approved by the institutional review boards at Stanford University and the Veterans Administration Palo Alto Health Care System. All participants signed an informed consent form prior to enrollment.

Intervention

Capnometry-assisted respiratory training is based on the idea that sustained levels of hypocapnia contribute to symptom development and maintenance of PD (13). The 4-week training included weekly 1-hour treatment sessions. The initial session included 1) educating patients about the exacerbation of panic symptoms through hypocapnia, 2) directing patients' attention to problematic respiratory patterns, 3) instructing patients to perform different breathing maneuvers with capnometer feedback to understand how changes in breathing affect physiological symptoms and mood, and 4) teaching patients how to modify PCO_2 and respiratory rate and instructions in between-session practices. Between-session exercises using a portable capnometer were to be performed twice daily for 17 minutes at home or elsewhere. The exercises consisted of three phases. Participants followed tape-recorded instructions that included time information and pacing tones. The baseline phase of the exercises was a 2-minute baseline during which patients sat quietly with their eyes closed. The paced breathing phase was a 10-minute paced breathing period during which patients breathed in synchrony with tones while occasionally checking their PCO_2 level and respiratory rate on a feedback device. The paced breathing served to guide patients to gradually slow their breathing across the weeks of treatment. The tones were set to correspond to a respiratory rate of 13 breaths per minute during the first week and rates of 11, 9, and 6 breaths per minute during successive weeks. The unpaced