Physiological Changes During Carbon Dioxide Inhalation in Patients With Panic Disorder, Major Depression, and Premenstrual Dysphoric Disorder

Evidence for a Central Fear Mechanism

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Background: Inhalation of carbon dioxide (CO₂) has been shown to produce more anxiety in patients with panic disorder (PD) than in healthy comparison subjects or patients with most other psychiatric illnesses tested, although premenstrual dysphoric disorder (PMDD) may be an exception. Several reasons have been proposed to explain CO₂ breathing effects in PD. We examined differences in respiratory response to CO₂ breathing in 4 groups to address these issues.

Methods: Patients with PD (n = 52), healthy controls (n = 32), patients with PMDD (n = 10), and patients with major depression without panic (n = 21) were asked to breathe 5% and 7% CO₂. Continuous measures of respiratory physiological indices were made.

Results: Carbon dioxide breathing produced the expected increases in all 4 respiratory variables measured. More patients with PD and PMDD had panic attacks than did controls or patients with major depression. Subjects who experienced panic during 5% or 7% CO₂ inhalation had the most extreme increases regardless of diagnostic group. Among patients with PD, baseline end-tidal carbon dioxide levels were significantly lower in those who subsequently had a panic attack during 5% CO₂ breathing than those who did not.

Conclusions: Although CO₂ breathing causes a higher rate of panic attacks in patients with PD than other groups (except PMDD), the physiological features of a panic attack appear similar across groups. Once a panic attack is triggered, minute ventilation and respiratory rate increase regardless of whether the subject carries a PD diagnosis. These findings are compatible with preclinical fear conditioning models of anxiogenesis.

Arch Gen Psychiatry. 2001;58:125-131

Many studies from multiple groups have now documented that patients with panic disorder (PD) are likely to experience panic attacks and greater anxiety than healthy volunteers during inhalation of carbon dioxide (CO₂). These attacks tend to be mild and end quickly when CO₂ inhalation is stopped.

At this point, it has been established that CO₂-induced panic is relatively specific to patients with PD, although patients with social phobia and with premenstrual dysphoric disorder (PMDD) may also be susceptible. It appears that CO₂-induced panic may be relatively resistant to cognitive manipulations or desensitization, although not all studies are compatible with this finding. Finally, rates of panic during CO₂ inhalation decline after successful treatment of panic disorder.

Despite the wealth of data that have accumulated concerning CO₂-induced panic, the mechanism of action and the neurobiological significance of this phenomenon are still obscure and also controversial. On the one hand, it has been argued that the susceptibility of patients with PD to high levels of anxiety during CO₂ breathing represents a specific abnormality in the afferent neural pathways that respond to increased levels of CO₂. Studies have shown that CO₂ sensitivity is increased in the clinically asymptomatic first-degree relatives of patients with PD, suggesting a familial and perhaps heritable abnormality.

On the other hand, it has been argued that because CO₂ breathing produces a sense of air hunger and breathlessness, it is highly reminiscent of the increased breathing and hyperventilation that are frequently experienced during naturally occurring panic. The non-specific somatic distress produced by CO₂ inhalation, according to this view, triggers the panic attack.

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The issue of whether CO₂-induced panic reveals a specific abnormality in the afferent sensory pathway or a non-specific somatic trigger could be resolved by performing formal respiratory sensitivity testing in patients with PD. Because studies, including our first 2, yielded different respiratory physiology results, leading to different conclusions, we thought it was important to complete one more study, with a third and independent cohort of patients with PD and controls. In addition, in the present study we also included a group of patients with major depression (MD), who generally do not respond to agents that produce panic in patients with PD, and a group of patients with PMDD, who were shown in a previous study to be sensitive to CO₂ breathing. The details of panic rate and anxiety generated during CO₂ breathing among the 4 groups are reported separately. Herein, we report on the ventilatory responses to CO₂ breathing. Two main questions are addressed: (1) Can we replicate one or the other of the findings of respiratory physiology differences during 5% or 7% CO₂ breathing between patients with PD and controls from the 2 earlier studies with this independent cohort? and (2) Is increased ventilatory response to CO₂ breathing specific to patients with PD or does it occur in any person having a panic attack regardless of diagnosis?
The experiment was divided into five 20-minute periods as follows: (1) room air breathing to establish a first baseline value, (2) 5% CO₂, (3) room air breathing to establish a second baseline value, (4) 7% CO₂, and (5) room air breathing to establish recovery to baseline value. Subjects were also shown how to open the canopy, which can be done in seconds by flipping a latch. In fact, none of the subject did this. Finally, subjects were instructed that if they felt they could not continue to breathe CO₂ they should raise their right hand and the flow of CO₂ would be stopped immediately.

ASSESSMENTS

Two assessments of whether a panic attack occurred were made following each of the CO₂ inhalation periods. The first was made by a rater blind to subject diagnosis who had been trained to reliably make the judgment of panic occurrence by viewing videotapes of lactate infusions. The blinded rater was instructed to use the DSM-IV criteria for a panic attack but was not permitted to ask the subject if he or she had experienced an attack. The second was made by the subject, who pointed to a card to answer whether a panic attack had occurred while the blinded rater was out of the room.

Four respiratory measures were collected continuously throughout the 5 periods: tidal volume, respiratory rate, minute ventilation (the product of tidal volume and respiratory rate), and end-tidal carbon dioxide (ETCO₂). Exhaled air for ETCO₂ measurement was sampled by a small nasal cannula sensor. Because the measurement may not be completely accurate if a subject exhales only through the mouth, a soft plastic mask was placed over the subject’s nose and mouth to ensure that all exhaled air passed by the ETCO₂ sensor. Heart rate and blood pressure data will be reported separately.

DATA ANALYSES

We wished to discern whether patients with PD have a different respiratory response to CO₂ than other groups and whether this is a function of having the disorder or of having a panic attack. The analysis is complicated because the very low rate of panic among patients with MD and healthy control subjects yields small cells for analyses broken down by diagnostic group and panic occurrence. To maximize the size of cells and still address the primary question, we performed as the main analysis a 2 (panic disorder vs all other groups combined) × 2 (panic vs no panic) × 6 (time points) repeated-measures analysis of covariance (RM-ANCOVA) for each of the 4 respiratory variables. The 6 time points represent the mean for the respiratory variable during the last 1 minute of the preceding baseline and the variable at minutes 1 through 5 of 5% CO₂ inhalation. After 5 minutes, the number of subjects in some cells declines to the point that analysis is no longer meaningful. This is because subjects were able to continue breathing CO₂ for varying lengths of time, with PD and PMDD patients always lasting the shortest length of time and controls and patients with MD the longest. Sex was the covariate. In this analysis, significant diagnostic group × time interactions would indicate differential respiratory responses to CO₂ in patients with PD compared with other groups; significant panic vs no panic group × time interaction would indicate differential respiratory response on the basis of whether an attack occurred; and a significant 3-way interaction would indicate differential respiratory response on the basis of both diagnosis and whether an attack occurred. Because previous work suggested that the blinded rater’s assessment was more useful for separating groups on the basis of differences in respiratory responses than the subject’s rating, we report analyses using the subject rating of panic only when they offer additional information.

In addition to the main analysis described here, which yields 4 RM-ANCOVA statistics, we performed a number of secondary analyses. These were a repeat of the strategy used for 5% CO₂ with data from the 7% CO₂ inhalation and a variant of the formal CO₂ sensitivity measure, the ratio of change in minute ventilation to change in ETCO₂ during CO₂ inhalation. For these analyses we used the last 5 minutes of baseline and the first 5 minutes during 5% and again during 7% breathing and performed a 4 × diagnostic group analysis of variance. This was repeated with change in tidal volume and change in respiratory rate as the numerators and an examination of whether first baseline respiratory measures were associated with subsequent panic to 5% CO₂. This was done by t tests for the last 5-minute baseline means of each of the 4 respiratory variables comparing all subjects who panicked with those who did not panic and then separately within each of the 4 diagnostic groups.

All tests are 2-tailed, with the significance level set at P < .05. When the Mauchly sphericity test was significant, the Greenhouse-Geisser correction of significance level was used.

RESULTS

SUMMARY OF PANIC RATES
AND TIME SPENT BREATHING CO₂

A total of 124 subjects entered the study. Seven subjects were dropped from the PMDD group because of failure to validate the diagnosis after prospective monitoring, leaving 117 subjects. Table 1 gives data on panic rates by blinded rater assessment for each of the 4 groups. Discrepancies in total sample size are due to missing data. One further subject had a panic attack during the first room air period and did not proceed further; therefore, 116 subjects actually breathed 5% CO₂. Of these, 7 subjects had a panic attack before 5 minutes, and data were excluded from 5 subjects because of technical problems. Therefore, data for analysis of respiratory variables during 5% CO₂ breathing are available from 104 subjects. Of the subjects with analyzable respiratory data, 44 had PD, 20 had MD, 8 had PMDD, and 32 were controls. As will also be reported in more detail elsewhere, the panic rates for both 5% and 7% CO₂ breathing are significantly greater for patients with PD than controls.
Table 1. Age, Sex, Distribution, Panic Rate, and Time Spent Inhaling Carbon Dioxide (CO2) Among the 4 Groups*  

<table>
<thead>
<tr>
<th>Variables</th>
<th>Panic Disorder (n = 52)</th>
<th>Healthy Controls (n = 34)</th>
<th>Major Depression (n = 21)</th>
<th>Premenstrual Dysorphic Disorder (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>32.0 ± 7.6</td>
<td>29.97 ± 8.1</td>
<td>34.33 ± 8.4</td>
<td>29.97 ± 8.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>29 (56)</td>
<td>19 (56)</td>
<td>11 (52)</td>
<td>0</td>
</tr>
<tr>
<td>Panic rate to 5% CO2</td>
<td>26 (52) [n = 50]†</td>
<td>3 (9)</td>
<td>3 (14)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Time spent inhaling 5% CO2, min</td>
<td>15.96 ± 6.94 [n = 51]†</td>
<td>19.66 ± 1.45</td>
<td>17.62 ± 4.71</td>
<td>15.10 ± 7.77</td>
</tr>
<tr>
<td>Panic rate to 7% CO2</td>
<td>32 (67) [n = 48]†</td>
<td>5 (16) [n = 32]†</td>
<td>7 (36) [n = 20]†</td>
<td>5 (56) [n = 9]†</td>
</tr>
<tr>
<td>Time spent inhaling 7% CO2, min</td>
<td>11.35 ± 7.34 [n = 48]†</td>
<td>17.06 ± 5.74 [n = 32]†</td>
<td>14.80 ± 6.91 [n = 20]†</td>
<td>11.11 ± 7.66 [n = 9]†</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD or number (percentage) of subjects.
†Change in sample size due to missing data points or subject did not enter this phase of study (see text for explanation).

There was no significant difference in panic rate between patients with MD or control subjects. However, patients with PMDD were susceptible to CO2-induced panic attacks at a rate similar to patients with PD, and these 2 groups were not statistically distinguishable in terms of panic rate.

Among the subjects with PMDD, 4 were tested in the lutal phase of the menstrual cycle, 6 in the follicular phase, and 5 in both phases. No distinction is made in any of the analyses with respect to phase of the menstrual cycle; for the few women with PMDD who were tested twice, we used only the first test regardless of cycle phase.

Table 1 shows the amount of time subjects actually breathed 5% and 7% CO2, broken down by group. Subjects with PD spent significantly less time breathing 5% CO2 than controls ($t_{172} = -3.89$, $P < .001$ by separate variance estimate) and significantly less time breathing 7% CO2 ($t_{172} = 3.90$, $P < .001$ by separate variance estimate).

Subjects with PMDD also spent significantly less time breathing 7% CO2 than controls ($t_{39} = 2.53$, $P = .02$).

**Physiological Response to CO2**

Figures 1, 2, 3, and 4 show minute ventilation, respiratory rate, tidal volume, and ETCO2 responses to 5% CO2 inhalation, respectively. Inspection of the figures shows that CO2 breathing produced the expected increases in all 4 respiratory variables. The 2-group (patients with PD vs other diagnosis) × 2-response (panic vs no panic) × time RM-ANCOVA yielded significant main effects for minute ventilation response for panic and time and significant interactions for group × panic and panic × time. The group effect and group × time interaction were not significant. Inspection of Figure 1 shows that subjects without PD who panicked had the most extreme reaction, followed by subjects with PD who panicked. The 2 groups of subjects who did
not panic, with or without PD, had virtually the same minute ventilation response. For respiratory rate, there were significant main effects for panic and time. Again, the main effect for group was not significant. For tidal volume, there were significant main effects for panic and time and a significant group × panic interaction. Here, the subjects without PD who panicked had a more extreme reaction than those with PD who panicked, those with PD who did not panic, and those with other diagnoses who did not panic. The latter 3 groups had virtually the same tidal volume response. Finally, for ETCO2, there were significant main effects for panic and time.

In summary, for all measures the response to 5% CO2 varied more with respect to whether a panic attack occurred than whether the subject had PD. Analyses of data from the 7% CO2 inhalation experiment are generally similar to the 5% CO2 inhalation experiment. For minute ventilation, there were significant main effects for time and panic and significant interactions for group × panic (F1,77 = 7.50, P = .008) and panic × time (F(1,77) = 4.09, P = .046) (data not shown but available on request from the authors). For respiratory rate, there was a significant panic × time interaction (F2,640 = 4.22, P = .009); for tidal volume, a significant main effect for panic; and no significant findings for ETCO2. The significant group × panic interaction for minute ventilation response to 7% CO2 is the only instance in which diagnostic group membership was a significant factor, but in this case the group with the most extreme reaction were those without PD who panicked. Hence, the data again indicate that having a panic attack was more important than having PD in distinguishing respiratory response.

None of the CO2 sensitivity analyses yielded significant differences among groups regardless of whether minute ventilation, tidal volume, or respiratory rate was used as the numerator.

Finally, Table 2 gives data and statistics for baseline respiratory measures broken down by panic status and diagnostic group. Although the t test was not significant for the entire sample, the ETCO2 was significantly lower in subjects with PD who panicked than in those with PD who did not panic (t187 = 4.267, P < .001, n = 48 by separate variance estimate). However, minute ventilation, respiratory rate, and tidal volume were significantly higher in subjects who panicked than in those who did not panic among the control and PMDD groups (data not shown).

COMMENT

These data fit with a growing body of studies that should influence theories about panic to CO2 and panic disorder neurobiology in general. Unlike our very first CO2 inhalation study, done a decade ago, we have now shown on 3 occasions that there is no difference in minute ventilation response to CO2 inhalation or in formal CO2 sensitivity between patients with PD and other groups. With this weight of data, substantiated by others, it is reasonable to consider theories that implicate central brain circuits rather than or in addition to abnormalities in the pulmonary, peripheral (aortic arch), or medullary chemoreceptor. It is clear that patients with PD have a substantially higher rate of panic attacks and develop more anxiety during CO2 inhalation than other groups, but there...
The present data suggest, therefore, that the panic response to CO₂ involves a generalized fear response that, although more common among patients with PD than almost any other diagnostic group or healthy controls, can still occur in people who do not have PD. This view gains further support from the association between lower baseline ETCO₂ and panic response to 5% CO₂ breathing. Such relative hypocapnia suggests that patients with PD who panicked when breathing 5% CO₂ were already anxious and hyperventilating before CO₂ inhalation started. Previously, we showed that low baseline PCO₂ levels, high cortisol levels, and increased anxiety are associated with panic to sodium lactate infusion.29 It should be noted, however, that increased respiration also predicted panic in 2 other groups in this study. Hence, baseline respiratory activity also seems to be a diagnostically nonspecific aspect of CO₂ panic. There is evidence that the tidal volume response to CO₂ inhalation is a genetically mediated function that reflects the sensitivity of the medullary chemoreceptor.30 The respiratory frequency response, on the other hand, is caused by the anxiety produced by the breathlessness and mechanical discomfort that occur when breathing CO₂. Interestingly, increase in respiratory rate rather than tidal volume distinguishes those who panic when breathing CO₂ from those who do not26,27 and is apparently the respiratory response to conditioned fear in experimental animals.31

We and others have noted the remarkable similarity between the physiological events that occur during stimulation of the amygdala in an experimental animal or human32-34 and those that occur during a panic attack.35,36 This has led to the widespread hypothesis that the neural circuit that subserves conditioned fear in animals may also be responsible, at least in part, for panic. The present findings with CO₂ inhalation fit this theory nicely. When asked to breathe CO₂, all subjects experience an obligatory increase in respiratory rate and tidal volume. This is tolerated by most individuals, even those with depression or obsessive-compulsive disorder. Patients with PD, however, experience the hyperventilation, breathlessness, and general somatic discomfort that they routinely experience during panic attacks. According to this view, CO₂ inhalation leads to stimulation of the neural circuit subserving fear in the patient with PD or any subject who panics, perhaps including activation of the amygdala and its projection sites. This causes, among other things, a greater increase in respiratory rate in the patient who panics compared with the patient who does not, further signaling danger and resulting in the panic attack itself.

To support this theory, it would be important to show that acute (short-term) fear in humans is accompanied by stimulation of the amygdala and other parts of the neural “fear” circuit and that patients with PD have an abnormally sensitive response in this circuit. This has been shown in healthy volunteers undergoing fear conditioning37 and in patients with social phobia during a cognitive challenge.38 Studies of patients with PD at rest indicate differences in activity compared with controls in limbic brain areas that include the hippocampus and the amygdala.39,40

There are a few methodologic shortcomings and theoretical objections that should be considered in interpreting our data. First, sample sizes in some of the cells are extremely small. This is due in part to the finding that control subjects and patients with MD rarely panic at CO₂ inhalation; therefore, hundreds of these subjects would have to be tested to yield a meaningfully larger number of patients who panic. Second, we recruited only a handful of patients with PMDD and did not control for phase of the luteal cycle. The analogy between a panic attack and the animal model of fear conditioning is not, to be sure, perfect. There is no evidence to date that PD is caused by conditioning; indeed, a requirement for the diagnosis of PD by DSM-IV is that the initial attack must be "spontaneous."

Carbon dioxide inhalation has proven to be a useful tool in understanding the cognitive and physiological characteristics of panic attacks. Furthermore, it is a medically benign procedure that is noninvasive and well tolerated. However, we believe that this study indicates its major limitation: ultimately, this type of CO₂ study can only inform us about peripheral and brainstem function. Clearly, PD is a complex illness that certainly involves higher brain regions. We believe that CO₂ studies have now pointed the way to the future of neurobiological research in PD that will require neuroimaging of cortical and subcortical sites. Nevertheless, our current data, the last in our series of studies examining the respiratory physiology associated with CO₂-induced panic, clearly suggest the importance of looking beyond peripheral explanations and attempting to integrate the human data with the vast array

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Table 2. Baseline Respiratory Measures for Patients With and Without Panic to 5% Carbon Dioxide in 4 Subject Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Panickers (n = 24)</th>
<th>Nonpanickers (n = 24)</th>
<th>Statistics</th>
<th>Panickers (n = 3)</th>
<th>Nonpanickers (n = 29)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV, L/min</td>
<td>5.33 ± 2.98</td>
<td>4.29 ± 2.36</td>
<td>t⁰ = 1.37; P = .18</td>
<td>7.04 ± 2.30</td>
<td>3.63 ± 1.49</td>
<td>t⁰ = 3.61; P &lt; .001</td>
</tr>
<tr>
<td>RR, /min</td>
<td>15.87 ± 3.25</td>
<td>15.79 ± 3.33</td>
<td>t⁰ = 0.09; P = .93</td>
<td>18.43 ± 0.22</td>
<td>16.44 ± 2.75</td>
<td>t⁰ = 3.78; P = .001†</td>
</tr>
<tr>
<td>TV, mL of air</td>
<td>375.72 ± 280.70</td>
<td>329.71 ± 237.10</td>
<td>t⁰ = 0.61; P = .54</td>
<td>306.76 ± 126.12</td>
<td>230.44 ± 93.05</td>
<td>t⁰ = 2.77; P = .01</td>
</tr>
<tr>
<td>EtCO₂, mm Hg</td>
<td>37.78 ± 5.22</td>
<td>43.15 ± 3.28</td>
<td>t⁰ = −4.27; P &lt; .001†</td>
<td>40.95 ± 4.21</td>
<td>42.11 ± 3.59</td>
<td>t⁰ = −5.29; P = .60</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD. MV indicates minute ventilation; RR, respiratory rate; TV, tidal volume; and EtCO₂, end-tidal carbon dioxide.
† t Separate variance estimate.
‡ n = 4.
## REFERENCES