Breath-holding in Panic Disorder

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In earlier studies, it was found that exogenous carbon dioxide administration provoked high anxiety in panic disorder (PD) patients, whereas healthy normals and patients suffering from other anxiety disorders were hardly affected. Breath-holding provides a simple method to induce endogenous CO_2 accumulation. Fourteen PD patients, 14 patients suffering from other anxiety disorders, and 14 healthy controls were asked to hold their breath as long as possible. Apnea times appeared to be longer in the normal control group than in the other two groups. Using a one-tailed *t* test, a trend for a difference was found between the PD subjects and other anxiety patients, the PD patients having slightly lower values. No differences were found with respect to increase in anxiety during breath-holding or the ratio of apnea times before and after hyperventilation.

VARIOUS METHODS of carbon dioxide administration have been described for provoking anxiety in panic disorder (PD) patients. Prolonged administration of a gas mixture containing 5% CO_2 has been demonstrated to induce panic in PD patients, whereas healthy controls seem to be hardly affected.[1-3] One vital capacity inhalation of a gas mixture with 35% CO_2 also rapidly triggers anxiety in PD patients, in contrast to normals, who experience only a slight increase in anxiety.[4] Furthermore, the 35% CO_2 challenge technique differentiates between PD and obsessive-compulsive disorder (OCD),[5] while panic attacks provoked by 35% CO_2 are not merely a consequence of increased baseline anxiety.[6]

These models concern exogenous administration of CO_2. A simple and natural method of inducing endogenous P_{CO_2} increase may be breath-holding. This technique has been used in disorders other than PD as a test for autonomic failure.[7] Bass et al. have reported that patients with chest pain and a normal electrocardiogram with a positive hyperventilation provocation test demonstrated a shorter breath-holding time than normal control subjects.[8] In patients with neurocirculatory dystonia (NCD), a syndrome possibly related to PD, Mäntysaari[9] used an extended version of a breath-holding test. This version had originally been developed by Friedman as a test to support the diagnosis of functional cardiovascular disease.[10,11] Subjects were asked to hold their breath as long as possible. Immediately after a 45-second period of hyperventilation, breath-holding was repeated and the ratio of these two breath-holding times, the "hyperventilation index" (HI) was calculated. Mäntysaari found that the ability to hold ones breath after a deep inspiration of air was similar in 30 male NCD subjects and 30 male normal controls, but the HI tended to be higher in normals than in NCD patients.[9]

The breath-holding test might be of interest in PD for two reasons. First, it provides a method to test a vulnerability to endogenous P_{CO_2} increase. Second, PD patients show signs of autonomic dysfunction,[12,13] even after successful psychological treatment.[14]

In the present study, we used the test as described by Mäntysaari.[9] Three groups of subjects were selected, one consisting of PD patients, another of patients suffering from other anxiety disorders, and finally a group of healthy controls. Since CO_2 inhalation appears to differentiate between PD on the one hand and other anxiety disorders and normal controls on the other, our hypothesis was that the breath-holding time would be shorter in PD patients than in other anxiety disorder subjects and normal controls. Moreover, it was expected that the HI would be lower in PD patients than in either other anxiety disorder patients or healthy controls. The goal of the present study was to explore whether breath-holding might serve as a simple test supporting the diagnosis of PD in patients with anxiety disorders. Therefore, we chose a design that was practical, uncomplicated, and easy to perform.

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METHOD

Subjects

Three groups of subjects participated in this study. The first group consisted of 14 PD patients with a mean age of 33.4 years (SD 7.24). The second group consisted of 14 patients suffering from another anxiety disorder with a mean age of 32.4 years (SD 10.3). Nine of these subjects were suffering from OCD, three from generalized anxiety disorder, and two from social phobia. The patients had been referred to the local Academic Anxiety Center Vijverdal and had been diagnosed by experienced clinicians using DSM-III-R criteria.[15] The third group consisted of 14 healthy control subjects with neither past nor current psychiatric problems and with a mean age of 32.5 years (SD 7.77).

Each group consisted of seven men and seven women, and all subjects were in good physical health and not under current psychiatric treatment. They had been free of medication that could possibly influence mental processes for at least 2 weeks, except for incidental use of low dosages of benzodiazepines (BZ). In the PD group, 10 subjects used no BZ, three used a daily dose equivalent to 5 or less mg diazepam per day, and one PD patient used BZ equivalent to 15 or less mg diazepam per day. In the other anxiety disorder group, 10 subjects used no BZ, two used BZ equivalent to 5 mg or less diazepam, and two used the equivalent of 10 or less mg diazepam. None of the normal controls used BZ.

Prior to the test, subjects were asked to refrain from alcohol for at least the preceding 8 hours, and from coffee, tea, or food for at least the preceding 2 hours.

Procedure

After explaining the procedure (in which the word "hyperventilation" was avoided), subjects were asked to complete a self-rating form to assess severity of the 13 panic symptoms listed in the DSM-III-R, each item ranging from 0 to 4. A total symptom score was calculated by adding the scores of the 13 items. In addition, subjective anxiety was quantified on a line of 100 mm, ranging from "no anxiety at all" to "the most terrifying experience one can imagine." Thereafter, subjects were asked to take a deep breath of a gas mixture containing 50% O_2 and 50% N_2, using a self-administration mask (Entonox, British Oxygen Company, England), and to hold the breath as long as possible. This O_2-enriched air was used to exclude possible limitations in breath-holding capacity due to hypoxia. The duration of apnea was measured, starting from the beginning of the deep breath. After breath-holding, subjects again completed the panic symptom list and pointed out their level of subjective anxiety, now referring to the period of breath-holding.

After 3 minutes, this procedure was repeated, but before holding their breath subjects had to hyperventilate for approximately 1 minute. Before and during hyperventilation, the end-tidal CO_2 pressure (PET CO_2) was measured with a Gould Godart Mk III capnograph (Gould Medical, Bilthoven, The Netherlands). During hyperventilation, an attempt was made to reduce the PET CO_2 to less than 50% of its baseline value. Subjective anxiety and panic symptoms were measured before hyperventilation and after breath-holding, the latter referring to the period of apnea.

For each breath-holding period, the increase of subjective anxiety and panic symptoms was calculated (value during apnea minus value before apnea). The HI was assessed by calculating the ratio of breath-holding time after and before hyperventilation.

RESULTS

Table 1 shows various parameters relevant to the first part of the test, i.e., before hyperventilation. There were no significant differences in age and gender distribution among the three groups. One-way analysis of variance (ANOVA) showed a significant difference in breath-holding time ($F = 6.673$, $df = 2,39$, $P = .003$). Corresponding two-tailed t tests showed a significant difference between PD patients and normals ($t = 3.65$, $df = 26$, $P = .001$) and a strong trend for a difference between patients with other anxiety disorders and normals ($t = 1.99$, $df = 26$, $P = .057$), while there was no difference between PD patients and patients with other anxiety disorders ($t = 1.58$, $df = 26$, $P = .126$). Using a one-tailed t test, a trend for a difference was found between PD patients and patients with other anxiety disorders ($P = .063$), the PD subjects having slightly lower breath-holding times.

Apnea times were also analyzed by nonparametric tests. The three groups differed significantly (Kruskal-Wallis, $P = .0048$). Healthy controls had significantly higher breath-holding times than both PD patients (Mann-Whitney U test, $P = .0012$) and other anxiety disorder sub-

Table 1. Means (±SD) of Various Parameters Before Hyperventilation

	PD (n = 14) [7 men/ 7 women]	Other Anxiety (n = 14) [7 men/ 7 women]	Normals (n = 14) [7 men/ 7 women]
Age (yr)	33.4 (7.24)	32.4 (10.3)	32.5 (7.77)
First breath-holding time (s)	34.4 (15.2)	48.6 (30.0)	74.4 (38.1)
Baseline anxiety	13.8 (12.19)	17.4 (21.88)	4.2 (5.74)
Baseline symptoms	3.43 (6.95)	2.71 (2.67)	0.29 (0.83)
Increase in anxiety	7.1 (10.38)	2.9 (10.50)	3.1 (7.49)
Increase in symptoms	1.07 (5.36)	1.14 (3.68)	4.36 (4.24)

jects (Mann-Whitney U test, $P = .0429$), whereas the PD and other anxiety disorder group showed no significant difference (Mann-Whitney U test, $P = .2693$).

Using one-way ANOVA, no differences were found with respect to baseline number of panic symptoms ($F = 2.033$, $df = 2,39$, $P = .145$) and increase in anxiety ($F = 0.847$, $df = 2,39$, $P = .436$). Trends for a difference were found for baseline anxiety ($F = 2.937$, $df = 3,39$, $P = .065$) and increase in number of symptoms ($F = 2.460$, $df = 2,39$, $P = .099$).

Pearson correlation coefficients (CC) between breath-holding time and the following parameters were calculated: baseline anxiety ($CC = -0.2929$, $P = .030$), baseline number of symptoms ($CC = -0.1105$, $P = .243$), increase in anxiety ($CC = -0.1288$, $P = .208$), and increase in symptoms ($CC = 0.4303$, $P = .002$).

Of the 42 subjects, 35 succeeded in decreasing their P_{CO_2} to 50% or less of the baseline value (Table 2). These subjects were included in a further analysis of breath-holding times after hyperventilation and calculation of HI. Although apnea times after hyperventilation provocation showed a highly significant difference ($F = 10.659$, $df = 2,32$, $P < .001$), the HIs were not significantly different ($F = 1.642$, $df = 2,34$, $P = .210$).

DISCUSSION

In the present study, PD patients and normal controls showed a significant difference in breath-holding times. This difference in apnea times could not be attributed to differences in sex distribution or age, since the groups were almost perfectly matched with respect to these factors. It was found that PD patients had significantly lower apnea times than normals. However, patients suffering from other anxiety disorders also tended to have lower breath-holding times than healthy controls. No significant difference was found between the PD and other anxiety disorder group (two-tailed t test, Mann-Whitney U), although there was a trend toward lower apnea times in PD patients than in patients with other anxiety disorders using a one-tailed t test. The increase in anxiety during breath-holding and the HI were not different among the three groups.

Table 2. Means (±SD) of Various Parameters After Hyperventilation Resulting in $P_{CO_2} \leq 50\%$ of Baseline Value

	PD (n = 11) [6 men/ 5 women]	Other Anxiety (n = 11) [5 men/ 6 women]	Normals (n = 13) [7 men/ 6 women]
Second breath-holding time (s)	61.3 (46.90)	75.7 (64.25)	159.2 (57.32)
HI	1.69 (0.587)	1.63 (1.154)	2.20 (0.710)

It seems that neither breath-holding nor the HI can serve as a simple test supporting the diagnosis of PD in patients with anxiety disorders. However, from a theoretical point of view, the results deserve further attention. To our knowledge, this is the first study reporting different breath-holding times between PD subjects and healthy controls. Since other anxiety disorder subjects also had shorter apnea times than normals, and both anxiety groups tended to have higher baseline anxiety than healthy controls, it seems obvious that anxiety and/or suffering from an anxiety disorder have contributed to decreasing breath-holding capacity. However, using a one-tailed t test, a trend for a difference in apnea times was found between PD and other anxiety subjects, PD patients having slightly lower breath-holding times. As these findings were found in rather small groups, significant differences might have been found in a larger sample size. If baseline anxiety has an effect of decreasing breath-holding times, it is the strongest in the groups with other anxiety disorders, since this group tended to experience highest baseline anxiety. In other words, if the PD and other anxiety groups had had the same level of baseline anxiety, the difference between these two groups would have become greater, possibly reaching statistical significance.

The expectation of a decreased breath-holding capacity in PD was based on our previous findings that the 35% CO_2 challenges provoked more anxiety in PD subjects than in patients suffering from other anxiety disorders.[5,6] However, the increase in subjective anxiety during breath-holding in the present study was small (Table 1) and not significantly different among the three groups. Probably, the CO_2 accumulation, due to breath-holding, was too small to provoke panic. It is likely that the subjects started breathing again well before the

point of panic was reached. Therefore, it could be argued that the breath-holding test is more comparable to assessment of ventilatory response to CO_2 (R_{CO_2}) than to panic provocation by means of CO_2. Data on R_{CO_2}, which is assumed to measure chemosensitivity to CO_2, unfortunately show conflicting results. Some studies find higher R_{CO_2} values in PD subjects than in normals,[16,17] whereas others do not show differences between PD and healthy subjects.[18-20] Comparison of breath-holding times with R_{CO_2} implicitly assumes that the endogenous CO_2 accumulation, as a consequence of breath-holding, is similar in each experimental group. However, many PD subjects seem to be in a continuous state of hyperarousal, as is reflected in, for instance, a raised resting heart rate and blood pressure.[12,13] Therefore, it could be argued that PD patients have a higher basal metabolism than normal controls, resulting in a greater CO_2 production in PD subjects than in normals. On the other hand, if higher endogenous CO_2 production was the only mechanism to explain the difference between PD patients and normals, it would seem logical that the increase in physical symptoms during breath-holding would be approximately equal in both groups. Subjects with higher endogenous CO_2 production would merely start breathing earlier, because they would reach a certain level of symptoms, forcing them to end apnea earlier. However, in the present study, PD subjects tended to experience less symptoms than normals and there was a positive correlation between breath-holding times and increase in somatic symptoms. Obviously, the longer subjects held their breath, the more symptoms they experienced. In other words, it seems that the reason why PD patients started breathing earlier than others cannot be attributed to a more rapid development of physical symptoms.

An alternative explanation for the present findings may be given by the concept of "fear of symptoms"[21] or "catastrophic misinterpretation."[22] According to these theories, various physical symptoms act as danger signals in PD subjects. Some of these symptoms, for instance, dyspnea, are provoked by breath-holding. To avoid experiencing these symptoms, PD patients would start breathing again as soon as these fearful physical symptoms began to appear. The finding that PD patients tended to have a smaller increase in physical symptoms than normal controls in the present study would support these cognitive mechanisms, although, on the other hand, other anxiety patients experienced a similar increase in symptoms as PD subjects.

Many factors may influence breath-holding, most of which could be controlled for in the present study. As already mentioned, the groups were almost perfectly matched with respect to sex distribution and age. The possible influence of P_{O_2} was controlled for by adding extra O_2 in the air that subjects inhaled before holding their breath.

It could be argued that the incidental use of BZ may also have affected the present results, as it is known that BZ may have an effect on both respiration and CO_2 sensitivity.[23,24] Only four subjects in each anxiety group used BZ, most of them in low dosages. If this BZ use has influenced the present results at all, it may have blurred the already clear distinction between normals on the one hand, and both anxiety groups on the other hand. Since BZ intake was approximately equal in both patient groups, it seems unlikely that it affected the difference in apnea times between PD and other anxiety subjects. In conclusion, PD patients, as well as subjects suffering from other anxiety disorders, were found to have shorter breath-holding times than normals. The results with respect to PD versus other anxiety patients are less clear, and warrant further investigation.

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