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PANIC DISORDER IN A BREATH-HOLDING CHALLENGE TEST

A simple tool for a better diagnosis

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ABSTRACT - *Objective*: Our aim was to observe if anxiety disorder patients – DSM-IV - respond in a similar way to the induction of panic attacks by a breath-holding challenge test. *Method*: We randomly selected 29 panic disorder (PD) patients, 27 social anxiety disorder (SAD) patients, 21 generalized anxiety disorder (GAD) patients. They were induced to breath-hold for as long as possible four times with two-minute interval between them. Anxiety scales were applied before and after the test. *Results*: A total of 44.8% (n=13) PD patients, 14.8% (n=4) SAD patients, 9.5% (n=2) GAD patients had a panic attack after the test (χ^2= 21.44, df= 2, p=0.001). There was no heart rate or anxiety levels difference among the groups before and after the test. *Conclusion*: In this breath-holding challenge test the panic disorder patients were more sensitive than other anxiety disorder patients.

KEY WORDS: panic attacks, respiration, anxiety disorder, comorbidity, ventilation.

Transtorno de pânico no teste da apnéia voluntária: uma ferramenta simples para um melhor diagnóstico

RESUMO - *Objetivo*: Nosso objetivo foi observar se os pacientes com transtorno de ansiedade – DSM-IV – respondem de maneira similar à indução de ataques de pânico através do teste da apnéia voluntária. *Método*: Selecionamos aleatoriamente 29 pacientes com transtorno de pânico (TP), 27 pacientes com fobia social (FS) e 21 pacientes com transtorno de ansiedade generalizada (TAG). Todos foram orientados à apnéia voluntária por quatro momentos consecutivos, com 2 minutos de intervalo, na maior duração possível. Escalas de avaliação de ansiedade foram utilizadas antes e após o teste. *Resultados*: 44,8% (n=13) pacientes com TP, 14,8% (n=4) pacientes com FS, 9,5% (n=2) pacientes com TAG tiveram ataques de pânico após o teste (χ^2= 21.44, df= 2, p=0,001). Não ocorreram diferenças entre os grupos em relação à freqüência cardíaca ou nível de ansiedade antes e após o teste. *Conclusão*: Nesse teste de apnéia voluntária os pacientes com transtorno de pânico foram mais sensíveis que os pacientes com outros transtornos de ansiedade.

PALAVRAS-CHAVE: ataque de pânico, respiração, transtorno de ansiedade, ventilação.

Respiratory abnormalities are associated with anxiety, particularly with panic attacks[1,2]. Symptoms such as shortness of breath, "empty-head" feeling, dizziness, paresthesias and tachypnea have been described in the psychiatric and respiratory physiology related to panic disorder[1,3]. Multiple lines of evidence implicate in biologic, especially respiratory, findings with anxiety disorders[3,4]. The respiratory challenge tests strategies have been particularly fruitful in generating hypotheses about panic disorder (PD)[5,6] and groups without panic disorder but with a high susceptible to respiratory induced panic attacks[7]. A number of agents are reported to be capable of provoking acute panic attacks in PD patients under laboratory conditions: carbon dioxide[8], sodium lactate[9], caffeine[10], isoproterenol[11] and yohimbine[11]. These agents induce panic attacks in the laboratory that are very similar of spontaneous panic attacks.

The inhalation of high concentrations of carbon dioxide (CO2) has consistently been shown to increase anxiety and induce panic attacks in PD patients[12,13]. Carbon dioxide induced panic attacks closely

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resemble the panic attack PD patients experience outside the laboratory[14]. Of the numerous agents capable of inducing panic attacks in PD patients, CO2 is one of the most reliable panicogenic agents[14]. Klein[15] proposed that spontaneous panic attacks occur when the brain's suffocation monitor erroneously signals a lack of useful air, maladaptively triggering an evolved suffocation alarm system. Such a dysfunction would make an individual vulnerable to "false suffocation alarms", namely panic attacks. Carbon dioxide sensitivity would be an aspect of a hypersensitive suffocation detector[15].

A simple and natural method of inducing endogenous CO2 increase may be the breath-hold. The provocation of anxiety by increase in CO2, as in breath holding, may be a reliable marker of panic. The understanding of the mechanisms involved in CO2-provoked anxiety could in turn shed light on the pathophysiology of PD. This agent probably triggers some vulnerability that may represent the predisposition to the development of panic. It has already been tested in some trials[16-19] but with different methodologies-no criteria for induced panic attack, various breath-holding tests and small samples - and poor discriminatory results. Perhaps these data could be explained by small and heterogeneous samples, diverse inclusion and exclusion criteria and unprecise panic attack criteria. Our experiment differed from them[16-19] as we used larger samples, three anxiety disorder groups - panic disorder (PD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD); restricted inclusion and exclusion criteria and a precise panic attack criteria.

Our aim was to observe if panic disorder patients (DSM-IV) respond in a similar way to the induction of panic attacks by a breath-holding challenge test. We also decided to try to discriminate panic disorder patients from other anxiety disorder patients as these groups might have some differences – physiological or psychopathological - in relations to the anxiety response level to the respiratory challenge test. We hypothesize that 1) the panic rates of panic disorder patients in response to the breath-holding challenge test will be greater than those of other anxiety disorder patients, 2) the panic rates of subjects with anxiety disorder but panic one will not differ significantly from each other. We expected that the panic disorder patients have a greater sensibility to this challenge test than the other groups.

METHOD

The period of selection was from June 2000 to December 2001. The patients who fullfiled an anxiety disorder diagnosis in their first visit to our center and were without any psychotropic medication for at least four weeks or fluoxetine for 5 weeks were invited to participate in our test. The protocol was explained to the subjects, who signed a voluntary written consent to participate in the study. The subjects were informed that they would be asked to breath-hold and that the procedure was not dangerous but anxiety symptoms could occur during the session. Our local Ethics Committee approved the protocol, which complied with the principles of the Declaration of Helsinki. Only after the acceptance and the written informed consent obtained, all the inclusion and exclusion criteria were checked. From a initial group of 187 anxiety disorder patients we selected 29 panic disorder patients, 18 women and 11 men; mean age ± SD: 36.8 ± 9.6 years; 27 social anxiety disorder patients, 15 women and 12 men; mean age ± SD: 42.8 ± 11.3 years; and 21 generalized anxiety disorder, 14 women and 7 men; mean age ± SD: 35.3 ± 15.0 in the Laboratory of Panic & Respiration of the Institute of Psychiatry, Federal University of Rio de Janeiro. All the subjects that participated in this study were not recruited for any other study. After anxiety disorder subjects received a clinical diagnosis made by a psychiatrist, they were interviewed by a second clinician blind for the first diagnosis with the Structured Clinical Interview Diagnostic – SCID[20] for DSM-IV[21]. If the two clinicians disagreed on the diagnosis, they met to confer. If a consensus on the diagnosis could not be reached, the subject was not enrolled. The SAD and GAD patients have not ever had a panic attack. Patients who met DSM-IV criteria for bipolar disorder, current major depression, schizophrenia, delusional or psychotic disorders, organic brain syndrome, severe personality disorder, epilepsy, or substance abuse or dependence (during the previous year) were excluded. Patients with comorbid dysthymia or past major depression were included if the anxiety disorder was judged to be the principal diagnosis. The inclusion criteria were: 18 to 55 years of age, occurrence of at least three panic attacks in the two weeks before the challenge test day just for PD patients, no use of any psychotropic drugs for at least five-week by any subject, and a negative urine test for benzodiazepines and other medications before the test. Exclusion criteria were: unstable medical condition, cognitive-behavior psychotherapy during the study; or the presence of suicidal risk. Subjects with a history of respiratory disease and current smokers were also excluded.

All subjects underwent physical examination and laboratory exams to ensure they were healthy enough to participate in a respiratory challenge test. They had no respiratory or cardiovascular abnormalities and were free of caffeine ingestion for one day. The test was conducted in the usual examination room, with no changes made in the environment. All subjects were asked to relax for 10 minutes. We then checked respiratory frequency, pulse and blood pressure and repeated the measurements 1 min and after the test. To measure the baseline anxiety level, before breath-holding subjects were asked to

complete the Subjective Units of Disturbance Scale (SUDS), a semiquantitative evaluation method ranging from 0 = no anxiety, to 10 = maximum anxiety[22], and the Diagnostic Symptom Questionnaire (DSQ)[22] adapted for DSM-IV in which the presence and level of discomfort of panic symptoms experienced after the test were rated on a 0 - 4 point scale (0= none, 4 = very severe). After the test the SUDS and DSQ were completed again. The subjects completed them independently of the raters. On the basis of the DSQ, a panic attack was defined by objective raters as the following: 1) four or more symptoms of a panic attack from the DSM-IV; 2) at least one of the cognitive symptoms of a panic attack from the DSM-IV (e.g. fear of dying or of losing sanity or control); 3) feeling of panic or fear, similar to spontaneous panic attacks recorded on a card which the raters were not permitted to observe; and 4) agreement at clinical diagnosis evaluation between two diagnosis blinded raters from the team during the test. The comparison of the two raters score was done after the test. The feeling of a panic attack reported by the subjects was also examined in order to compare agreement between raters and subjects. The results were divided in raters score (all the four items of the panic attack criteria) and subjects score (just the first three items of panic attack criteria).

We explained to the subjects what they were expected to do. The breath-holding test consisted of four trials as used by Van der Does[16]. The first three trials each had a 1 min anticipation period, followed by cessation of brething at functional residual capacity for maximum duration, and a 2 min recovery period. Subjects were instructed to stop breathing following a normal (i.e. not forced) exhalation and maintain the cessation for as long as possible. The fourth trial constituted breath holding after a full vital capacity breath. All patients used an easily self-removable nose-clip. Immediately before the test and just after it we made the evaluation of the anxiety level and the induction of a panic attack. Immediately after this period we evaluated the level of anxiety and the induction of a panic attack. A chronometer was used for measuring the breath-hold time.

Table 1. Response of patients with panic disorder (PD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD) challenged with a breath-holding test.

Rating after breath-holding	PD n=29	SAD n=27	GAD n=21
Raters*			
Panic	13 (44.8%)	4 (14.8%)	2 (9.5%)
No panic	16 (55.2%)	23 (85.2%)	19 (90.5%)
Subject**			
Panic	14 (48.3%)	4 (14.8%)	1 (9.5%)
No panic	15 (51.7%)	23 (85.2%)	20 (90.5%)

*χ^2= 22.44, df= 2, p=0.001. (PD vs SAD. χ^2 with Yates correction= 0.97 p=0.055), (PD vs GAD. χ^2 with Yates correction= 1.59 p=0.003), (SAD vs GAD. Fisher exact test, 2-tailed p=0.251). ** χ^2= 26.99, df= 2, p=0.001. (PD vs SAD. χ^2 with Yates correction= 0.89 p=0.051), (PD vs GAD. χ^2 with Yates correction= 1.74 p=0.004), (SAD vs GAD. Fisher exact test, 2-tailed p=0.341).

Statistical analysis. Panic rates for the three groups, also separated according to rater and subject ratings and by gender were compared by the chi-square test. Data concerning the effects of breath-holding and time of observation were tested by two-way ANOVA with repeated measures for time and independent groups for SUDS (before and after) and heart rate (before and after). Pair wise comparisons of the treatment groups were performed at end-point; using Fisher's protected least significant difference method. For identifing heart rate difference among groups a one-way ANOVA was used for time difference using Fisher's protected least significant difference method. The level of significance was set at 5%.

RESULTS

Table 1 shows the panic rates assigned by the raters and by the subjects during the challenge test. Significantly more PD patients had a panic attack in response to breath-holding than other anxiety disorder patients according to both rater groups: a total of 44.8% (n=13) PD patients, 14.8% (n=4) SAD patients, 9.5% (n=2) GAD patients had a panic attack after the test (χ^2= 21.44, df= 2, p=0.001). There was no significant sex difference in any group (χ^2= 0.56, df=2, p=0.678).

Table 2 shows the Subjective Units of Disturbance Scale level measurement before and after breath-holding test. PD patients were not more sensitive to the effect of breath-holding than other anxiety disorder groups. There were no statistical difference among the groups (two-way ANOVA, the group by time interaction: F= 1.283, df=2.84, p= 0.238). All groups showed an increase in anxiety levels after the test.

There was no group difference in maximum breath-hold times (sec) among groups: PD= 78.5 ± 34.9; SAD= 81.3 ± 40.59; GAD= 75.2 ± 29.6 (ANOVA. F= 0.768 df=2 p=0.874).

All groups had a similar heart rate before (1 minute before) breath holding (one-way ANOVA, F= 0.275, df =2, p= 0.894). There was no time effect

Table 2. Subjective anxiety levels just before and after the breath-holding challenge test (mean ± SD). Panic disorder (PD), social anxiety disorder (SAD), and generalized anxiety disorder (GAD).

Self-rating	PD n=29	SAD n=27	GAD n=21
SUDS before	3.8 ± 2.3	3.7 ± 2.0	2.9 ± 2.2
SUDS after	5.6 ± 3.4	4.8 ± 2.5	4.2 ± 2.3

SUDS. Subjective Units of Disturbance Scale. Two-way ANOVA.The group by time interaction: F= 1.283, df=2.84, p= 0.238. The effect of time: F= 1.565 df=2.84, p=0.311. (Fisher's protected least significant difference: PD vs SAD p=0.435; PD vs GAD p= 0.527; SAD vs GAD p=0.787).

on heart rate and a time group interation, demonstrating no heart rate-time interaction between groups (two-way ANOVA, group by time interaction with Greenhouse-Geisser correction: F= 0.256, df=2. 332, p=0.813).

DISCUSSION

Our main finding is the clear differentiation of PD patients from other anxiety disorders by a simple respiratory test. The precise and clinical criteria for induced panic attack may be the crucial point for our results. The data support Klein's theory[15,23] and suggest that the breath-hold test may be a marker for some patients. Carbon dioxide sensitivity might be higher in respiratory PD subtype patients and would be an aspect of a hypersensitive suffocation detector. Respiratory symptoms may also play an important role in real life panic attacks and in CO2-induced panic attacks.

This study compares panic disorder patients with anxiety disorder patients in a breath-holding challenge test. Our results indicate that those subjects who have PD are more likely to panic in response to the breath-holding challenge test. The findings from this study could be examined in two ways: whether panic patients experience more symptoms following breath-holding or whether they interpreted their symptoms following breath-holding more severely than the other groups. The strength of our study is the inclusion of other anxiety disorder groups. We found no sex difference in the anxiety response among our groups. Perhaps these breath-holding - sensitive PD patients will be clearly identified in the future with a more sophisticated methodology. Bovasso and Eaton[24] tried to differentiate of three types of panic attacks for understanding the course and etiology of panic. They identified types were consistent over time and for which reliable scales were constructed to measure derealization, cardiac panic, and respiratory panic. The respiratory panic disorder subtype may be the most sensitive one to respiratory challenge tests than the others. Our anxiety patients and the control subjects reported similar symptoms and we observed a similar heart rate sugesting that PD patients may perceive these symptoms to be more aversive, perhaps resulting in a greater likehood to panic. The distinction between anxiety disorders versus PD would be relevant as one might expect greater catastrophic cognitions in the latter as opposed to the former group. In another study[25] with the same methodology we observed in this breath-hold challenge test PD patients (n=26) were more sensitive to breath-hold than first-degree relatives (n=28) and normal volunteers (n=25). Our data suggested there is no association between family history of PD and hyperreactivity to a breath-hold challenge test.

The voluntary breath holding was not found previously as a suitable test to measure suffocation alarm threshold in some PD studies. Asmundson and Stein[17] compared the duration of breath holding in PD (n=23), generalized social phobia (n=10), and healthy subjects (n=26). PD had a significant shorter breath-holding duration than either comparison group but all groups did not differ in physiology response. Roth et al.[18] studied a 12 times repeated 30 seconds breath-holding test and also did not find any physiological support for a sensitive suffocation alarm system in PD. Van der Does[16] investigated voluntary breath holding in PD patients, mood disorder patients and normal controls. There was no difference in mean breath-holding durations. Zandbergen et al.[19] tested the breath-hold in a small sample PD patients (n=14), patients with other anxiety disorders (n= 14) and 14 healthy controls. Apnea times appeared to be longer in the control group. No differences were found with respect to increase in anxiety during breath holding. Perhaps our results were different because we used more restricted inclusion and exclusion criteria, the PD patients were severe ones with current spontaneous panic attacks, we used clinical scales and criteria instead of just physiological measures and our criteria for panic attack were clearly specified.

The evidence implicating respiratory abnormalities in the pathogenesis of panic attacks is rapidly accumulating. Panic disorder patients seem to be more sensitive to breath-holding test than other anxiety disorder patients. The suffocation false alarm[15,23] as well as the CO2 hypersensitivity may act in conjunction with cognitive factors to induce panic attacks in panic disorder patients. It is need to establish in which group of panic disorder patients breath-holding is a specific test; whether it varies with age or sex of the patients and to what extent they are cognitively mediated.

Our data suggest there is an association between PD and panic attacks in this breath-holding test. Other anxiety disorder - SAD and GAD - may be differentiated from PD by this respiratory test in respect to the induction of panic attacks.

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