

## PANIC DISORDER AND HYPERVENTILATION

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**ABSTRACT** - Respiratory abnormalities are associated with anxiety, particularly with panic attacks. 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. Panic disorder patients exhibit both behaviorally and physiologically abnormal responses to respiratory challenges tests. Objective: We aim to observe the induction of panic attacks by hyperventilation in a group of panic disorder patients (DSM-IV). Method: 13 panic disorder patients and 11 normal volunteers were randomly selected. They were drug free for a week. They were induced to hyperventilate (30 breaths/min) for 3 minutes. Anxiety scales were taken before and after the test. Results: 9 (69.2%) panic disorder patients and one (9.1%) of control subjects had a panic attack after hyperventilating ( $p < 0.05$ ). Conclusion: The panic disorder group was more sensitive to hyperventilation than normal volunteers. The induction of panic attacks by voluntary hyperventilation may be a useful and simple test for validating the diagnosis in some specific panic disorder patients.

**KEY WORDS:** panic attack, respiration, anxiety disorder, ventilation.

### Transtorno do pânico e hiperventilação

**RESUMO** - Distúrbios respiratórios estão associados à ansiedade, especialmente aos ataques de pânico. Sufocamento, sensação de "cabeça leve", tonteira, parestesias e taquipnéia aparecem na descrição psiquiátrica e respiratória do transtorno do pânico. Pacientes com transtorno do pânico apresentam respostas comportamentais e fisiológicas anormais a testes respiratórios. Objetivo: Observamos a indução de ataques de pânico através de hiperventilação em um grupo de pacientes com transtorno do pânico (DSM-IV). Método: Selecionamos de forma randomizada 13 pacientes com transtorno do pânico e 11 voluntários normais. Todos estavam sem medicação há uma semana. Foram induzidos a hiperventilar (30 inspirações/minuto) durante 3 minutos. Escalas de ansiedade foram utilizadas antes e após o teste. Resultados: No grupo com transtorno de pânico, 9 (69,2%) pacientes apresentaram ataque de pânico após a hiperventilação e apenas 1 (9,1%) no grupo controle ( $p < 0,05$ ). Conclusão: Os pacientes com transtorno do pânico foram mais sensíveis à hiperventilação que o grupo controle. A indução de ataques de pânico através da hiperventilação pode ser método útil e simples para validar o diagnóstico em um grupo específico de pacientes com transtorno do pânico.

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

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One of the features of the description of a panic attack is the physical nature of the symptoms. Patients with panic disorder always begin the description of their disease mentioning either the respiratory system, the heart or the gastrointestinal tract<sup>1</sup>. Symptoms such as shortness of breath,

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“empty-head” feeling, dizziness, paresthesias and tachypnea have been described in the psychiatric and respiratory physiology related to panic disorder<sup>2,3</sup>. Respiratory abnormalities are associated with anxiety, particularly with panic attacks<sup>1,2</sup>. Panic patients reported significantly more panic attacks and anxiety during the challenges than normal volunteers<sup>1,4</sup>. Panic disorder patients exhibit both behaviorally and physiologically abnormal responses to respiratory challenge tests<sup>4,5</sup>.

Hyperventilation is an increase in the amount of inhaled and exhaled air per minute, exceeding the amount necessary for normal cell metabolism. Hyperventilation encompasses the state where ventilation exceeds cellular metabolism, resulting in an elimination of CO<sub>2</sub> greater than its production, which causes a decline in arterial partial pressure of carbon dioxide (PCO<sub>2</sub>)<sup>1,5</sup>. During exercises the amount of CO<sub>2</sub> produced increases as a result of an increased cell metabolism, but the PCO<sub>2</sub> remains constant because alveolar ventilation also increases, which is responsible for an increase in CO<sub>2</sub> elimination<sup>1,3</sup>. Hyperventilating at 30 breaths a minute, in spite of significant drops in end-tidal CO<sub>2</sub> to conventionally accepted levels of hypocapnia, seemed less convincing panicogenic challenge than CO<sub>2</sub><sup>6,7</sup>. However, a group of panic disorder patients can have in hyperventilation a safe, easy and specific test for a more precise diagnosis.

Our aim is to determine in induced panic attacks using room air hyperventilation (30 breaths/minute) during 3 minutes in panic disorder patients if there is any difference when compared to a control group.

## METHOD

We have randomly selected by order of arrival the 13 panic disorder patients (8 women and 5 men; mean age = 31.9 years, sd = 6,5) at the Laboratory of Panic & Respiration of the Institute of Psychiatry from the Federal University of Rio de Janeiro. The comparison group consisted of 11 subjects (6 women and 5 men, mean age = 30.5 years, sd = 11.7). The diagnosis was obtained using the Structured Clinical Interview – SCID I<sup>8</sup> for DSM-IV<sup>9</sup> and the patients should not fulfill the criteria for any other psychiatry disorder. They were explained about the study and signed a voluntary written consent for their participation in this study which informed that they would be asked to hyperventilate room air and that the procedure was not dangerous but anxiety or panic could occur during the study. The protocol complying with the principles laid down in the Declaration of Helsinki was approved by our local Ethics Committee.

To participate in the study the subjects were required to be between the ages of 18 and 55 years and to report at least three panic attacks in the two weeks before the challenge test day. They were free of psychotropic drugs for at least one week and have a negative urine test for benzodiazepines and other medications. All patients underwent a physical examination and laboratory tests to ensure they were healthy enough to participate in a hyperventilation challenge test. They should have no previous history of respiratory diseases and had never smoked.

The comparison group were also assessed by the SCID – I<sup>8</sup>. They were free of any lifetime history of anxiety disorders, major mood disorders, schizophrenia, and current substance use disorders. All subjects underwent medical evaluations and were in good health.

The whole test was conducted at the usual examination room, with no changes made in the environment. The selected patients were induced to relax for 10 minutes. After this period we checked the respiratory frequency and blood pressure. To measure the baseline anxiety level, subjects were asked before hyperventilating to complete the Subjective Units of Disturbance Scale (SUDS), a semiquantitative evaluation method ranging from 0 = no anxiety, 10 = the maximum anxiety<sup>10</sup>, and the Diagnostic Symptom Questionnaire - DSQ<sup>11</sup> adapted for DSM-IV in which the presence and level of discomfort of panic symptoms experienced after the inhalations were rated on a 0 - 4 point scale (0 = none, 4 = very severe). After the test the SUDS and the DSQ were completed again. They completed them blindly to the raters.

On the basis of the Diagnostic Symptom Questionnaire, a panic attack was defined as the following: 1) four or more symptoms of a panic attack from DSM-IV; 2) at least one of the cognitive symptoms of a panic attack from DSM-IV (e.g. fear of dying or of losing sanity); 3) feeling of panic or fear, similar to spontaneous panic attacks answered on a card which the raters were not permitted to observe; and 4) clinical evaluation by two diagnosis blinded raters from the team during the test.

Table 1. Response of patients with panic disorder and normal comparison subjects challenged with room air hyperventilation

Rating after Hyperventilation	Panic Disorder (n=13)	Normal Control (n=11)
Raters*		
Panic	9	1
No panic	4	10
Subject**		
Panic	7	1
No panic	6	10

\*McNemar's Test with Yates correction. Chi-square= 12.5, df= 3, p<0.05, \*\*McNemar's Test with Yates correction. Chi-square= 13.6, df= 3, p<0.05

Table 2. Subjective anxiety levels just before and after hyperventilating.

Self-rating	Panic disorder (n=13)	Normal control (n=11)
SUDS before	2.5 ± 4.0*	1.9 ± 2.4**
SUDS after	5.7 ± 3.1*	3.7 ± 2.3**

SUDS, subjective units of disturbance scale.

\*Friedman two-way ANOVA, Student-Newman-Keuls Method., df = 1, F= 3.549, p= 0.107

\*\*Friedman two-way ANOVA, Student-Newman-Keuls Method., df = 1, F= 4.212, p= 0.083

Afterwards we induced hyperventilation (30 respiratory movements per minute during 3 minutes), and immediately after this period we made the evaluation of the anxiety level and the induction of a panic attack.

#### Data Analysis

Rates of panic among the two groups, also separated for raters' and subjects' ratings and by gender were compared with the McNemar's test. For the effects of the hyperventilation and time of observation were tested by Friedman two-way ANOVA on ranks according to the results of Kolmogorov-Smirnov (with Lilliefors' correction) test for normality and Levene median test for variances. When pairwise multiple comparisons were required, Student-Newman-Keuls method was applied. The significant level was set at 5%.

## RESULTS

Table 1 shows the panic rates during the interventions according to the raters and to the subjects. Significant more panic patients had a panic attack in response to hyperventilation than the group control by using either ratings. 9 (69.2%) panic disorder patients, one (9.1%) of control subjects had a panic attack after hyperventilating ( $X^2 = 12.5$ , df=3, p< 0.05). There was no significant sex difference in any group ( $X^2 = 4.18$ , df=1, p=ns).

In Table 2 there is the Subjective Anxiety Level measure by SUDS before and after hyperventilating. Patients with panic disorder although not statistically significant seemed to be more sensitive to hyperventilation effects than normal volunteers. All subjects had an increase in anxiety levels after hyperventilating .

## DISCUSSION

Some methodological improvements can be made in order to increase the hyperventilation challenge test sensibility. A more vigorous hyperventilation test would show better results but it would otherwise increase noncompliance in panic disorder patients. The comparison between panic disorder patients and a control group or other anxiety disorder group may be useful for a better defining symptoms and diagnosis. Our results confirm the hyperventilation challenge test (30 breaths per minute during 3 minutes) as a useful and easy diagnostic tool for some specific panic disorder patients differentiating them from normal controls, increasing diagnostic validity.

Although we found neither sex nor anxiety response difference among the groups, these hyperventilating sensitive panic disorder patients may be clearly identified in the future with a more sophisticated methodology.

Papp et al.<sup>5</sup> showed that hyperventilation is a relatively mild panicogenic agent. During voluntary hyperventilation patients with panic disorder often recognize some of the symptoms felt

during a panic attack<sup>12,13</sup>. For this reason hypocapnia may be an important factor in anxiety that occurs during a panic attack and hyperventilation<sup>4,7</sup>. These data suggest that hyperventilation do occur during some panic attacks.

We also observed that some clinical findings of this syndrome (anxiety, faster or deeper breathing, palpitations, tachycardia, dizziness, tremors, feelings of panic, unease, fatigue, crying spells, paresthesias) are similar to the clinical findings in panic disorder, and many of its symptoms are part of the diagnostic criteria for panic attacks from the DSM classifications.

Although hyperventilation frequently occurs it may be not a cause or an important component in panic attacks. Several other studies do not give support to the theory that hyperventilation arouses panic attacks or contributes to its severity<sup>5,15</sup>. It may be that hyperventilation is a consequence of panic attacks in hyperventilation predisposed individuals<sup>4,15,16</sup>. Zanbergen et al.<sup>14</sup> looked for evidencies of chronic hyperventilation in 18 patients with panic disorder (DSM-III-R) measuring arterial PCO<sub>2</sub>, base excess, bicarbonate (HCO<sub>3</sub>) and pH from these patients. Comparing this data with those found in 18 healthy controls and 12 patients with other anxiety disorders (obsessive-compulsive disorder, social phobia and generalized anxiety disorder) there were no significant differences found out in the base excess or HCO<sub>3</sub> levels between patients with Panic Disorder, other anxiety disorders and healthy controls. This result also suggests that there is no systematic chronic hyperventilation in patients with panic disorder. Bonn et al<sup>17</sup> studied panic attacks provocation by hyperventilation with 21 patients who had the diagnosis of agoraphobia with panic attacks and with 47 normal controls. All the patients were asked to make 60 respiratory movements per minute, during 3 minutes. The authors found out that 20 (95%) of the 21 patients affirmed that the symptoms felt at the laboratory were similar to those felt in their spontaneous panic attacks, although most of them affirmed that the symptoms felt at the laboratory were less intense. All the controls felt some dizziness, paresthesias and the sensation of "being light". They confirm the prominent role of hyperventilation in agoraphobia with panic attacks, according to the authors.

There is not a methodological coherence between the various studies mentioned above. Some do not inform if the panic disorder patients are in acute symptomatic period, others do not describe wash-out periods and many times the diagnostic criteria for panic attacks are not informed. Gorman et al<sup>12</sup> studied 12 patients with panic disorder or agoraphobia with panic attacks (DSM-III). The patients were asked to hyperventilate (30 respiratory movements/minute) for 15 minutes. After the test the patients filled in the Acute Panic Inventory, which measures the severity of the typical panic symptoms. They found out that 3 (25%) of the 12 patients have had panic attacks after this procedure, demonstrating that the induction of a respiratory alkalosis would not be enough to provoke panic attacks in all patients. Hyperventilation is a probable cause for panic attacks in a percentage of patients with panic disorder<sup>1,7,14</sup>. The losses to patients with panic disorder and their families justify greater investments in its research for a more precise diagnosis.

According to the cognitive approach<sup>18</sup> the catastrophic interpretation of bodily sensations induced by hyperventilation would have a greater role in the panic attack. The erroneous interpretation of bodily sensations as dangerous and threatening would result in an increase in anxiety, which in turn would lead to new sensations, and thus result in a vicious circle until the panic attack. The respiratory re-training techniques may reduce the severity of the symptoms during the panic attack by decreasing the hyperventilatory response<sup>5,18</sup>.

Our previous study<sup>19</sup> with a CO<sub>2</sub> challenge test in panic disorder patients suggest the efficacy of the short term clonazepam therapy in attenuating panic attacks and support the usefulness of the 35% carbon dioxide challenge test as an analogue method for study the efficacy of anti-panic drugs. For sure both test needs more research with a large number of patients to help elucidate the neurobiologic vulnerability of panic disorder patients and may lead to the development of more specific and effective treatments.

## CONCLUSION

Hyperventilation has been considered as a cause, a correlate and a consequence of panic attacks. Future studies will establish in which group of panic disorder patients the hyperventilation challenge test is a specific tool for diagnosis; whether it varies with age or sex of the patients and to what extent they are cognitively mediated. The evidence implicating respiratory abnormalities in the pathogenesis of panic is rapidly accumulating. While our data presented here support a theory<sup>20</sup> advocating that some panic disorder represents a primary respiratory abnormality, these remain a number of critical areas in need of exploration before such assertion can be fully validated.

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