Respiratory manifestations of panic disorder: causes, consequences and therapeutic implications*

Aline Sardinha, Rafael Christophe da Rocha Freire, Walter Araújo Zin, Antonio Egidio Nardi

Abstract

Multiple respiratory abnormalities can be found in anxiety disorders, especially in panic disorder (PD). Individuals with PD experience unexpected panic attacks, characterized by anxiety and fear, resulting in a number of autonomic and respiratory symptoms. Respiratory stimulation is a common event during panic attacks. The respiratory abnormality most often reported in PD patients is increased CO₂ sensitivity, which has given rise to the hypothesis of fundamental abnormalities in the physiological mechanisms that control breathing in PD. There is evidence that PD patients with dominant respiratory symptoms are more sensitive to respiratory tests than are those who do not manifest such symptoms, and that the former group constitutes a distinct subtype. Patients with PD tend to hyperventilate and to panic in response to respiratory stimulants such as CO₂, triggering the activation of a hypersensitive fear network. Although respiratory physiology seems to remain normal in these subjects, recent evidence supports the idea that they present subclinical abnormalities in respiration and in other functions related to body homeostasis. The fear network, composed of the hippocampus, the medial prefrontal cortex, the amygdala and its brain stem projections, might be oversensitive in PD patients. This theory might explain why medication and cognitive-behavioral therapy are both clearly effective. Our aim was to review the relationship between respiration and PD, addressing the respiratory subtype of PD and the hyperventilation syndrome, with a focus on respiratory challenge tests, as well as on the current mechanistic concepts and the pharmacological implications of this relationship.

Keywords: Panic disorder; Anxiety; Respiration; Hyperventilation; Carbon dioxide.

Resumo

Múltiplas anormalidades respiratórias podem ser encontradas em pacientes com transtornos de ansiedade, particularmente no transtorno de pânico (TP). Indivíduos com TP experimentam ataques de pânico inesperados, caracterizados por ansiedade, medo e diversos sintomas autonômicos e respiratórios. A estimulação respiratória é um fenômeno comum durante os ataques de pânico. A anormalidade respiratória mais citada em pacientes com TP é a sensibilidade aumentada para o CO₂, que originou a hipótese de uma disfunção fundamental nos mecanismos fisiológicos de controle da respiração no TP. Há evidências de que pacientes com TP com sintomas respiratórios predominantes são mais sensíveis a testes respiratórios do que aqueles sem a manifestação de tais sintomas, representando um subtipo distinto. Pacientes com TP tendem a hiperventilar e a reagir com pânico como resposta a estimulantes respiratórios como o CO₂, gerando uma ativação de um circuito de medo hipersensível. Apesar de a fisiologia respiratória desses pacientes permanecer normal, algumas evidências recentes apontam a presença de disfunções subclínicas na respiração e em outras funções relacionadas à homeostase corporal. O circuito do medo, composto pelo hipocampo, córtex pré-frontal medial, amígdala e projeções do tronco cerebral, pode estar hipersensível em pacientes com TP. Essa teoria pode explicar porque os medicamentos e a terapia cognitivo-comportamental são claramente eficazes. Nosso objetivo foi revisar a relação entre respiração e TP, especialmente o subtipo respiratório de TP e a síndrome da hiperventilação, focalizando os testes respiratórios, bem como as hipóteses mecanísticas e as implicações farmacológicas dessa relação.

Descritores: Transtorno de pânico; Ansiedade; Respiração; Hiperventilação; Dióxido de carbono.

* Study carried out in the Laboratory of Panic and Respiration at the Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB/UFRJ, Institute of Psychiatry of the Federal University of Rio de Janeiro) and at the Instituto Nacional de Ciência e Tecnologia (INCT, National Institute of Science and Technology) – Translational Medicine – Rio de Janeiro, Brazil.

Correspondence to: Aline Sardinha. Laboratório de Pânico e Respiração, Av. Venceslau Brás, 71 Fundos, CEP 22290-140, Urca, Rio de Janeiro, RJ, Brasil.

Tel 55 21 9417-2708. E-mail: alinesardinhaipsi@gmail.com

Financial support: This study received financial support from the Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, National Council for Scientific and Technological Development) and the Fundação de Apoio à Pesquisa do Estado do Rio de Janeiro (FAPERJ, Foundation for the Support of Research in the State of Rio de Janeiro).


** A versão completa em português deste artigo está disponível em www.jornaldepneumologia.com.br
Introduction

Respiration and its control mechanisms play a prominent role in generating abnormal anxiety, particularly panic disorder. A panic attack typically begins with a sudden, unexpected rise of terror, accompanied by a number of autonomic, especially cardiorespiratory symptoms. Panic disorder has long been the focus of research into the relationship between the respiratory system and anxiety disorders.

The hyperventilation syndrome seen during panic attacks has been characterized as having a chronic and an acute form. In this conceptual model, it is thought that disturbed breathing causes bursts of hyperventilation and respiratory alkalosis, triggering various somatic signs and symptoms, such as dizziness, tremors and palpitations, which precipitate fear and anxiety. Klein proposed the existence of an evolved “false suffocation alarm” system that triggers spontaneous panic attacks when the brain erroneously signals a lack of useful air and activates maladaptive autonomic responses to suffocation. Sensitivity to CO₂ might play a role in this hypersensitive suffocation detector, and various respiratory tests, such as carbon dioxide inhalation, hyperventilation and breath-holding, have been fruitful in generating hypotheses about panic disorder. Panic disorder patients exhibit behavioral and physiological abnormal responses to respiratory challenge tests that are very similar to those experienced during spontaneous panic attacks. This phenomenological characterization of panic attacks and the response of panic disorder patients to the respiratory tests led to the subtyping of such patients. Briggs et al. identified a subgroup of panic disorder patients presenting prominent respiratory symptoms, characterized by a greater number of spontaneous panic attacks, a better response to antidepressants, greater sensitivity to CO₂ challenge and greater overall severity of the disorder.

The objective of this review was to describe the close relationship between panic disorder and respiration, in order to provide scientific data to guide the decision-making process in daily clinical practice. We address panic disorder with prominent respiratory symptoms, as well as the results of respiratory challenge tests. Therapeutic implications and current mechanistic concepts for panic disorder are also discussed.

Hyperventilation syndrome

In hyperventilation syndrome, there are complex interactions among organic, respiratory, psychiatric and physiological disturbances. Anxiety disorders, such as panic disorder, are associated with mild hyperventilation and other breathing pattern abnormalities. There is a bidirectional association between hyperventilation and anxiety, as evidenced by the fact that individuals with idiopathic hyperventilation have been shown to score higher on anxiety and depression scales than do control subjects. Hyperventilation can therefore be considered a cause, a correlate and a consequence of panic attacks.

Acute hyperventilation can produce anesthesia, paresthesia, ataxia, tremor, tinnitus, cold extremities, palmar hyperhidrosis, giddiness, loss of consciousness, visual disturbances, headache and chest pain. There is therefore symptom overlap between panic disorder and hyperventilation syndrome, since panic attacks include most of these symptoms, together with others, such as breathlessness, feeling of choking, nausea, derealization (an alteration in the perception or experience of the external world that makes it seem strange or unreal), depersonalization (an alteration in the perception or experience that causes a feeling of detachment from the mental processes or the body), fear of dying and fear of losing control.

The prevailing hypothesis to explain the symptom overlap between acute hyperventilation and panic disorder is that panic disorder patients suffer from chronic episodes of hyperventilation, in which they shift toward hypocapnic alkalosis as a consequence of stress-induced acute hyperventilation, generating panic attacks. There are three major experimental findings to support that idea. First, panic attacks and hyperventilation syndrome both feature dyspnea, palpitations, tremors, paresthesia and giddiness. Second, hyperventilation syndrome overlaps with panic disorder in approximately 40% of patients. Finally, the acute hyperventilation challenge test, in which patients hyperventilate (30 breaths/min) for 4 min, reproduces panic-like symptoms in a significant proportion of panic disorder patients.

Stress-induced hyperventilation produces symptoms that are frequently misinterpreted as life-threatening by patients who are unaware...
of the consequences of overbreathing.\textsuperscript{(13)} Misinterpretation of these symptoms increases fear and activates the autonomic nervous system, thus increasing respiratory frequency, which causes further CO\textsubscript{2} washout and intensifies the hypocapnic symptoms.\textsuperscript{(14)} This creates a positive feedback loop, increasing the panic response and giving rise to a panic attack.

One of the leading organic causes of hyperventilation syndrome is asthma.\textsuperscript{(10)} In one sample of asthma patients, 36% were found to suffer from hyperventilation syndrome.\textsuperscript{(14)} In that study, the majority (78%) of the asthma patients with hyperventilation syndrome were women. In addition, the patients with asthma and hyperventilation syndrome more often presented with basal dyspnea, were more sensitive to anxiety and more often sought emergency room treatment for exacerbations.

Asthma has also been correlated with panic disorder and other psychiatric comorbidities, independent of the degree of asthma severity.\textsuperscript{(15)} Asthma patients with panic disorder report illness-specific and generalized panic/fear more often than do those without panic disorder. Asthma patients reporting illness-specific panic/fear also report poorer health-related quality of life, including emotional disturbance. Illness-specific panic/fear has been associated with more primary care office visits for asthma, greater irritability during asthma attacks, increased restriction of activities and greater use of rescue medication.\textsuperscript{(14)}

It is possible that hypocapnia induced by hyperventilation creates symptoms that asthma patients cannot control by using asthma medication, and that their perceived control over the management of their disease is therefore impaired.\textsuperscript{(16)} Clinical anxiety and panic manifestations affect symptom perception and asthma management directly, due to the effects of anxiety symptoms such as hyperventilation, and indirectly, due to changes in self-management behavior and physician response. Therefore, behavioral interventions designed to improve quality of life and treatment response among such patients should be tested.\textsuperscript{(17)}

**Underlying mechanisms of panic disorder**

**Increased CO\textsubscript{2} sensitivity**

There are two lines of evidence suggesting that panic attacks originate in the brain stem.\textsuperscript{(13)} The first advances the idea that the nature of the symptoms can be explained by a

---

Figure 1 - Panic attack mechanisms.
surge of impulses from the autonomic nervous system. The second line of evidence is related to the CO₂-mediated experimental provocation of panic attack itself, since CO₂ primarily affects the brain stem, especially the respiratory center, located in the reticular substance of the medulla oblongata and the pons.\(^{(1)}\)

Klein\(^{(5)}\) proposed that panic attack results from the dysregulation of a phylogenetically evolved alarm system directed at monitoring signals of suffocation. This alarm system has been evolutionarily programmed to be activated when there are metabolic signs of asphyxia and impending death. As a survival alert system, this suffocation monitor most likely serves a deeply rooted adaptive function, being activated only in extreme life-threatening circumstances. The Klein hypothesis might help us understand the preeminence of respiratory symptoms in panic attacks. One drawback of the hypothesis is that no “false suffocation alarm” system has been anatomically or functionally identified as such within the central nervous system. Attempts to identify the panic circuitry in the brain should focus on the chemosensitive areas of the central nervous system.

Considering the hyperoxic nature of the substances used in CO₂ challenge, any stimulating influence of the peripheral oxygen chemosensitive areas can be ruled out. Studies evaluating increased ventilation after the inhalation of increasing concentrations of CO₂—which would indicate dysfunction at the level of the chemosensitive areas of the central nervous system—have yielded contradictory results.\(^{(3)}\) This could be partly explained by a lack of control for confounding variables and by the well-known wide interindividual variability in CO₂ sensitivity.

Although we understand that intermittent hypoxia can have a different effect in panic disorder patients than in healthy controls, we have yet to identify the specific mechanism by which panic disorder patients are exposed to this phenomenon. There is some evidence that chemosensitive areas of the central nervous system related to panic responses extend to several brain stem nuclei, including the nucleus tractus solitarius, the locus coeruleus and the raphe nuclei, all of which are within the broad brain stem respiratory network.\(^{(3)}\) These structures should logically be considered as the best candidates for the functional role of suffocation detector. In addition, panic disorder patients appear to lose a certain degree of effective homeostatic control after their physiological equilibrium has been disrupted by a respiratory stressor.\(^{(10)}\)

**Genetic predisposition**

The influence of genetics on CO₂-induced panic has also been studied. It has been suggested that CO₂ sensitivity reflects a trait marker that runs in families.\(^{(19)}\) Hence, CO₂ sensitivity can be considered a phenotypic expression of an underlying genetic predisposition that can exist before the clinical onset of panic disorder.\(^{(20)}\) The proposed genetic mechanisms include differential expression of chemoreceptors and its influence on neurotransmitter systems. The ultimate isolation of genetic markers could lead to preventive measures for vulnerable individuals. It remains unknown whether CO₂ sensitivity and the resulting hyperventilation are characteristic of all normal subjects or only of panic disorder patients. It is possible that CO₂ sensitivity is related to a specific subtype of panic disorder, is

---

**Chart 1 - Practical applications of each respiratory test.**

<table>
<thead>
<tr>
<th>Respiratory test</th>
<th>Procedure</th>
<th>Diagnostic accuracy</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>30 breaths/min for 4 min</td>
<td>++</td>
<td>Panic attacks with predominant respiratory symptoms in half of panic disorder patients</td>
</tr>
<tr>
<td>Breath-holding</td>
<td>Three trials of cessation of breathing after unforced exhalation, 2-min recovery period. Fourth trial: breath-holding after inhalation up to vital capacity</td>
<td>+</td>
<td>Shorter breath-holding time in panic disorder patients; lower end-tidal PaCO₂ and anxiety</td>
</tr>
<tr>
<td>CO₂ inhalation</td>
<td>A single inhalation up to vital capacity of a gas mixture containing 35% CO₂ and 65% oxygen</td>
<td>+++</td>
<td>Neurovegetative panic-like symptoms in normal subjects. Panic attacks in most of panic disorder patients.</td>
</tr>
</tbody>
</table>
a hypersensitive homeostatic response (the “false suffocation alarm”) or is simply an indirect cause of panic by means of nonspecific irritation of any number of chemical or mechanical receptors.

Many authors have found that healthy relatives of panic disorder patients are significantly more likely to react to CO\textsubscript{2} challenge than are healthy subjects without a familial history of panic disorder. The authors of one study found that the rates of CO\textsubscript{2}-induced panic attacks suggested an association between hypersensitivity to CO\textsubscript{2} and genetic predisposition to panic disorder.\textsuperscript{[21]} Those authors concluded that panic disorder patients and individuals genetically predisposed to panic disorder are at an increased risk for experiencing smothering symptoms. In that same study, the risk of developing panic disorder was found to be significantly higher for patients who were hypersensitive to CO\textsubscript{2} than for subjects with normal reactivity to CO\textsubscript{2} (14.4\% vs. 3.9\%), suggesting that hypersensitivity to CO\textsubscript{2} is associated with a subtype of panic disorder specifically related to greater genetic predisposition.\textsuperscript{[21]} In addition, the authors stated that CO\textsubscript{2} challenge has predictive value, since relatives of panic disorder patients with respiratory symptoms presented an approximately three-fold higher risk for panic and a nearly six-fold higher risk for panic with smothering symptoms in comparison with relatives of panic disorder patients without respiratory symptoms.\textsuperscript{[21]}

Taken together, the results of these studies support the idea that the panic-respiration connection might foster a further step in the quest to identify a valid gold standard for use in determining panic disorder phenotype. Hypersensitivity to CO\textsubscript{2} bears a relevant genetic component and seems to be significantly related to genetic predisposition to panic disorder. In addition, CO\textsubscript{2} hypersensitivity might represent the phenotypical expression of genetic predisposition to panic disorder, even when clinically absent. Therefore, subjects with CO\textsubscript{2} hypersensitivity or respiration abnormalities might be considered “affected” members in molecular genetic studies. Alternatively, hypersensitivity to CO\textsubscript{2} could be considered the phenotypic expression of one of the genes involved in the respiratory panic disorder subtype. Therefore, the “true” phenotype for genetic studies could be defined solely by clinically expressed panic and CO\textsubscript{2} hypersensitivity. If the etiology of panic disorder is strongly related to genetic factors and CO\textsubscript{2} hypersensitivity is linked to the pathogenesis of panic disorder, it can be presumed that CO\textsubscript{2} hypersensitivity is modulated by genetic influences. This hypothesis is supported by the results of a study of twins,\textsuperscript{[22]} in which the rate of CO\textsubscript{2}-induced panic attacks was found to be significantly higher in monozygotic twins than in dizygotic twins (55.6\% vs. 12.5\%).

**The central nervous system hypothesis**

It is possible that panic disorder is caused by dysfunctions in the serotonergic, opioid and gamma-aminobutyric acid systems. Although far from being confirmed, the assumption that abnormalities in neurotransmitters found in panic disorder reflect altered brain function is based on the effectiveness of drugs that modulate neurotransmitters (e.g., serotonin) in the treatment of panic disorder. The serotonergic system influences the behavior of many brain areas involved in the regulation of body functions, and serotonin receptors have been found in many organs other than the brain. There is considerable evidence linking the serotonergic system to peripheral respiratory function. Serotonin transporters are expressed in human...
pulmonary membranes and are important in the maintenance of upper airway patency in obstructive sleep apnea.\(^2\)\(^3\)\(^4\) Sertraline, a selective serotonin reuptake inhibitor, reduces dyspnea in patients with COPD,\(^5\)^ and paroxetine relieves respiratory symptoms in patients with obstructive sleep apnea.\(^6\)

The endogenous opioid system has been recognized as an important regulator of the central respiratory drive.\(^7\) When the opioid receptors are stimulated, CO\(_2\) sensitivity reduces and the respiratory rate slows. Conversely, the opioid receptor antagonist naloxone increases the ventilatory response to hypercapnic hypoxia in normal human subjects.\(^8\) Opioid deficiency could explain why lactate induces panic attacks.\(^9\) To explore this hypothesis, one group of authors administered intravenous naloxone and sodium lactate to twelve normal controls.\(^9\) Although none of the subjects felt anxious, experienced fear or had a panic attack, they all presented with panic symptoms and increased tidal volume.

Recent studies analyzing the neurobiology of conditioned fear responses have employed a model of panic disorder that attempts to integrate neurochemical, neuroimaging and treatment findings with mostly preclinical data.\(^1\)\(^3\)\(^9\) Panic attacks are thought to originate from an abnormally sensitive fear network, centered in the central nucleus of the amygdala (CNA). The sensory input for the conditioned fear stimulus runs through the anterior thalamus to the lateral nucleus of the amygdala, thence to the CNA, where all the information is gathered and the autonomic and behavioral responses are coordinated. The CNA sends stimuli to the following structures: the parabrachial nucleus, increasing respiration rate;\(^9\) the lateral nucleus of the hypothalamus, activating the sympathetic nervous system; the locus coeruleus, increasing norepinephrine release, blood pressure, heart rate and the behavioral fear response; and the paraventricular nucleus of the hypothalamus, increasing the release of adrenocorticotropic hormone. A projection from the CNA to the periaqueductal gray region is responsible for additional behavioral responses, including defensive behaviors and postural freezing.

Although the amygdala receives direct sensory input from brain stem structures and the sensory thalamus, enabling a rapid response to potentially threatening stimuli, it also receives afferents from cortical regions involved in the processing and evaluation of sensory information.\(^3\)\(^9\) There are also important reciprocal connections between the amygdala and the sensory thalamus, prefrontal cortex, insula and primary somatosensory cortex. A neurocognitive deficit could result in a misinterpretation of sensory information, leading to inappropriate activation of the fear network via misguided excitatory input to the amygdala.

A deficiency in the coordination of the stimuli from the cortex and brain stem could lead to abnormal activation of the amygdala, with behavioral, autonomic and neuroendocrine stimulation. Panic originates from within an abnormally sensitive fear network, which includes the prefrontal cortex, insula, thalamus and amygdalae, as well as amygdalar projections to the brain stem and hypothalamus.\(^1\)\(^3\)\(^9\)

Evidence supporting this idea has emerged from recent neuroimaging studies indicating that the amygdala, anterior cingulate cortex and insula play a crucial role in the pathophysiology of anxiety disorders.\(^3\)

In addition to the evidence of strong connections between the amygdala and the carotid body, it has been suggested that the direct sensitivity of amygdala to acid-base changes, together with the interconnections between the amygdala and the parabrachial nucleus,\(^3\) constitute an alternative pathway linking respiratory signals to panic.\(^3\) The potential role of hypoxia as a marker of asphyxia, as well as the suggested sensitivity of panic disorder patients to anoxia, is supported by evidence from animal studies reporting that the amygdala and the hippocampus are particularly sensitive to anoxic stimulation. A summary of the panic attack process can be seen in Figure 1.

### Diagnostic challenge tests

The various diagnostic challenge tests are compared in Chart 1.

**Hyperventilation**

The acute hyperventilation challenge test (30 breaths/min for 4 min) can reproduce panic-like symptoms in a significant proportion of panic disorder patients.\(^9\) In a previous study,\(^7\) our group described the clinical features
of hyperventilation-induced panic attacks in panic disorder patients and compared them with their spontaneous panic attacks, as well as with spontaneous panic attacks in panic disorder patients not sensitive to the hyperventilation challenge test. Of the 88 panic disorder patients evaluated, 45 (51.1%) developed a panic attack after hyperventilating. Patients who panicked during the test more often had a family history of mental disorder, were older at the disorder onset and more often had a history of depressive episodes. The spontaneous and induced panic attacks were very similar in the subjects that exhibited a panic attack. However, in those that did not develop panic after hyperventilating, the spontaneous panic attacks were more often accompanied by chills/hot flushes and much less often accompanied by respiratory symptoms such as shortness of breath, choking sensation, chest pain/discomfort, paresthesia and fear of dying. In another study, involving a one-week self monitoring period, the hyperventilation-induced panic attack group subjects reported greater frequency and severity of respiratory symptoms, meeting the criteria for the respiratory panic disorder subtype.

Although these data seem to support a causal role for hyperventilation, there is some evidence against it, and a growing number of studies question the ability of acute hyperventilation to induce panic attacks. Such studies suggest that, although hyperventilation can induce a certain degree of anxiety, it cannot induce a reaction similar to spontaneous panic attacks in panic disorder patients. It is, however, unquestionable that some panic disorder patients present symptoms related to hyperventilation, as also suggested by the evidence of a relationship between the severity of hyperventilation-induced anxiety symptoms and a gradual decrease in cerebral blood flow in response to hypocapnia-induced alveolar hyperventilation. Finally, many studies have shown that hypocapnia definitely has a stronger panicogenic effect than hyperventilation, although there is as yet no consensus.

**Breath-holding**

The breath-holding challenge test, which is a simple method of increasing endogenous CO₂, increases PaCO₂ and decreases PaO₂, resulting in chemoreceptor stimulation and a strong drive to resume breathing. Van der Does developed a breath-holding test that consists of four trials. Each of the first three trials has a 1-min anticipation period, followed by cessation of breathing at functional residual capacity, and a 2-min recovery period. In these instances, the subjects are instructed to stop breathing, then exhale normally (i.e., unforced exhalation), and remain in apnea for as long as possible. The fourth trial consists of breath-holding after inhalation up to vital capacity. A stopwatch is used to measure the breath-holding time. The level of anxiety before and after the test is evaluated, as are panic disorder symptoms.

According to the Klein hypothesis, panic disorder patients are more sensitive to a rise in CO₂ and should not be able to hold their breath for long. The breath-holding time has been found to be shorter, and the end-tidal PaCO₂ to be lower, in panic disorder patients than in normal controls, demonstrating the lower tolerance to CO₂ in the former group. Increased anxiety and panic attacks during the breath-holding procedure has been described.

**CO₂ challenge**

Among the numerous agents capable of inducing panic attacks in panic disorder patients, CO₂ represents one of the most reliable panicogenic agents. One group of authors observed that subjects with panic disorder, in contrast with healthy controls, develop a panic-like reaction within minutes after beginning to breathe a gas mixture containing 5% CO₂. Panic attacks induced by CO₂ have been associated with cardiorespiratory activation including increased respiratory rate and blunted tidal volume response, as well as tachycardia and increased blood pressure. An alternative method of CO₂ challenge involves a single vital capacity inhalation of a gas mixture containing 35% CO₂ and 65% oxygen. Under these conditions, healthy subjects present with brief but pronounced respiratory stimulation accompanied by neurovegetative symptoms that largely overlap with those reported by panic patients. In panic disorder patients, the same intervention also induces a sharp, transient rise in anxiety that has been equated with a real life panic attack. Administered in a controlled laboratory environment, the single-breath 35% CO₂ challenge is a brief test whose effects dissi-
Respiratory manifestations of panic disorder: causes, consequences and therapeutic implications

In one study, 15 (93.7%) of 16 respiratory panic disorder subtype patients and 5 (43.4%) of 11 non-respiratory panic disorder subtype patients had a panic attack during one of two CO₂ challenges. In another study, comparing 117 panic disorder patients of the respiratory and non-respiratory subtypes, using the 35% CO₂ challenge test and the hyperventilation test, 80.3% and 53.0% of the patients in the respiratory subtype group had a panic attack in response to CO₂ challenge and the hyperventilation test, respectively. However, only 11.8% of the non-respiratory subtype patients had a panic attack during the CO₂ challenge, and 33.3% had a panic attack during the hyperventilation test.

These findings provide an innovative perspective on panic disorder treatment, respiration-focused interventions being proposed and tested to treat panic disorder patients. A recent study provided preliminary evidence that raising end-tidal PaCO₂ by means of capnographic feedback is therapeutically beneficial for panic disorder patients with moderate to large effect sizes. In addition, breathing training that targets PaCO₂ seem to reduce fear of bodily sensations in panic disorder patients.

Pharmacologic implications

The results of some studies have suggested that anti-panic drugs modulate respiratory physiology. Twelve weeks of anti-panic treatment with tricyclic antidepressants, imipramine and clomipramine in particular, have been found to significantly decrease CO₂ sensitivity (as expressed by minute ventilation and end-tidal CO₂) in patients with panic disorder, whereas no significant changes are detected in healthy subjects. Similar results were obtained with clomipramine as well as with selective serotonin reuptake inhibitors such as fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram. High-potency benzodiazepines have repeatedly been shown to decrease panic/anxiety responses to hypercapnic gas mixtures. Monoamine oxidase inhibitors also reduce CO₂ reactivity.

It is noteworthy that consumption of alcohol diminishes CO₂ sensitivity in panic disorder patients, a finding that sheds light on the high rates of alcohol abuse in panic disorder.
There is evidence that the respiratory and the non-respiratory subtypes respond differently to pharmacological interventions. Patients belonging to the respiratory subtype present better improvement with imipramine, whereas patients belonging to the non-respiratory subtype respond better to the high-potency benzodiazepine alprazolam. In addition, respiratory subtype patients have been shown to respond earlier to treatment with nortriptyline (a second-generation tricyclic antidepressant) than do non-respiratory subtype patients, the former presenting a response after only 8 weeks, although both groups had improved equally after 52 weeks. Similar behavior has been observed for the high-potency benzodiazepine clonazepam.

Final considerations

There is a substantial amount of data demonstrating that respiratory stimulation is a common event in panic disorder patients during a panic attack. Certain respiratory abnormalities, such as enhanced CO₂ sensitivity and thoracic respiration have been detected in panic disorder patients. As a result, it seems that there is a fundamental abnormality in the physiological mechanisms that control breathing in panic disorder. Accumulated evidence suggests that respiratory physiology remains normal in panic disorder patients, and that their tendency to hyperventilate and to panic in response to panic disorder patients, and that their tendency to hyperventilate and to panic in response to panic disorder might explain why medication and cognitive-behavioral therapy are both clearly effective. Although it remains unclear whether the abnormal function underlying panic attacks lies in the limbic system, and therefore primarily related to fear, or in the brain stem, and therefore principally related to a primal emotion, it must be borne in mind that there are complex relationships between these two brain areas. Therefore, in broad terms, panic disorder should be viewed as the complex result of multiple interactions between various brain networks. The evidence of abnormalities in several neurochemical systems might simply be an expression of the complex interaction among brain circuits. Consequently, attempts to focus on one isolated component of this complex array as the pathogenetic system of panic disorder are apparently unwarranted.

References

12. Nardi AE, Valença AM, Nascimento I, Zin WA. Hyperventilation challenge test in panic disorder
Respiratory manifestations of panic disorder: causes, consequences and therapeutic implications


About the authors

Aline Sardinha
Clinical Psychologist. Laboratory of Panic and Respiration at the Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB/UFRJ), Institute of Psychiatry of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

Rafael Christophe da Rocha Freire
Physician. Laboratory of Panic and Respiration at the Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB/UFRJ), Institute of Psychiatry of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

Walter Araújo Zin
Researcher. Laboratory of Respiration Physiology at the Carlos Chagas Filho Institute of Biophysics, Universidade Federal do Rio de Janeiro (UFRJ), Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

Antonio Egidio Nardi
Associate Professor. Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB/UFRJ), Institute of Psychiatry of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.