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ARTICLE

Panic disorder and the respiratory system: clinical subtype and challenge tests

Rafael C. Freire,[1] Antonio E. Nardi[1]

[1] Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro, National Institute for Translational Medicine (INCT-TM), Rio de Janeiro, Brazil

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Abstract:
Introduction: Respiratory changes are associated with anxiety disorders, particularly panic disorder (PD). The stimulation of respiration in PD patients during panic attacks is well documented in the literature, and a number of abnormalities in respiration, such as enhanced CO_2 sensitivity, have been detected in PD patients. Investigators hypothesized that there is a fundamental abnormality in the physiological mechanisms that control breathing in PD. *Methods:* The authors searched for articles regarding the connection between the respiratory system and PD, more specifically papers on respiratory challenges, respiratory subtype, and current mechanistic concepts. *Conclusions:* Recent evidences support the presence of subclinical changes in respiration and other functions related to body homeostasis in PD patients. The fear network, comprising the hippocampus, medial prefrontal cortex, amygdala and its brainstem projections, may be abnormally sensitive in PD patients, and respiratory stimulants like CO_2 may trigger panic attacks. Studies indicate that PD patients with dominant respiratory symptoms are particularly sensitive to respiratory tests compared to those who do not manifest dominant respiratory symptoms, representing a distinct subtype. The evidence of changes in several neurochemical systems might be the expression of the complex interaction among brain circuits.

Corresponding author: Rafael Christophe Freire; Laboratory of Panic and Respiration; Universidade Federal do Rio de Janeiro; Rua Visconde de Pirajá, 407/702, 22410-003, Rio de Janeiro, RJ, Brazil; Phone: (+55 21) 25216147; E-mail: rafaelcrfreire@gmail.com

Introduction

Respiratory changes are associated with anxiety, particularly with panic attacks (PA) and panic disorder (PD).[1,2] Researchers have attempted to understand the connection between PD and respiratory system[3] and elucidate the neurobiological circuit that underlies PAs, and hence shed light on the causes of pathological anxiety states.[4-6]

Klein[4] proposed that spontaneous PAs occur when the brain's perception of suffocation erroneously signals a lack of air, inappropriately triggering the alarm system derived from suffocation. Such dysfunction would make an individual vulnerable to "false suffocation alarms", namely PAs. Respiratory tests have been fruitful in generating hypotheses about PD,[3,4] indicating that CO_2 sensitivity would be part of a hypersensitive suffocation detector.[4] PD patients exhibit both behavioral and physiological abnormal responses to respiratory challenge tests.[7,8] Symptoms such as shortness of breath, "empty-head" feeling, dizziness, paresthesias and tachypnea have been described in psychiatry and respiratory physiology in relation to PD.[1,9] PD patients report significantly more PAs and anxiety during respiratory challenges than normal volunteers.[1,10,11] A number of agents have been reported as capable of provoking acute PAs in PD patients under laboratory conditions, including some respiratory challenge tests with carbon dioxide,[12] hyperventilation,[13] and breath-holding.[14] These laboratory tests can induce PAs that are very similar to spontaneous PAs. The inhalation of high concentrations of CO_2 has consistently been shown to increase anxiety and induce PAs in PD patients.[15,16] Among the numerous agents capable of inducing PAs in PD patients, CO_2 represents one of the most reliable panicogenic agents.[17]

The phenomenological characterization of PAs and the response of PD patients to the respiratory tests led Briggs et al.[18] to describe a subgroup of PD patients with prominent respiratory symptoms that presented more spontaneous PAs and responded better to antidepressants, while other patients had more situational PAs and responded better to benzodiazepines. In this line of thought, Biber et al.[19] found that PD patients with prominent respiratory symptoms were more sensitive to the CO_2 challenge test, had a significantly longer duration of illness, more severe panic and phobic symptoms, and were more likely to be heavier smokers than patients with non-respiratory symptoms.

The objective of this review is to describe the close relationship between PD and respiration; to present the findings of the respiratory challenge tests (hyperventilation and CO_2) and their power do discriminate PD patients from normal controls and other anxiety disorder patients; to discuss, in detail, panic disorder with prominent respiratory symptoms; and also to discuss the current mechanistic concepts: increased CO_2 sensitivity, exaggerated cerebrovascular responses to hypocapnia, abnormalities of the central rhythm generator, and neurobiological abnormalities.

Diagnostic challenge tests

Hyperventilation

The acute hyperventilation challenge test may reproduce panic-like symptoms in a significant percentage of PD patients,[20] and hyperventilation, i.e., breathing in excess to the metabolic requests, is often found in association with PAs.[21] Respiration and its control mechanisms may play a prominent role in generating abnormal anxiety, particularly PD.[22] Analyses locating respiratory disturbances at the core of PAs are quite recent.[4,23,24] Since then, the amount of data supporting and deepening the understanding of a connection between the vital function of breathing and PD has persistently accumulated.[3]

Some authors support the causal role of hyperventilation in the development of PAs:[13] PD patients may have chronic hyperventilation that shift to hypocapnic alkalosis as a consequence of stress-induced acute hyperventilation, thus yielding PAs. This hypothesis has been built over three main experimental evidences. First, PAs and the "hyperventilation-syndrome" show common symptoms, such as dyspnea, palpitations, tremors, paresthesias, and faintness. Second, the hyperventilation syndrome has been reported to overlap with PD in about 40% of patients.[25] Third, the acute hyperventilation challenge test, in which patients hyperventilate (30 breaths per minute) during 4 minutes, reproduces panic-like symptoms in a significant percentage of PD patients.[13,20] A growing number of studies questions the ability of acute hyperventilation to induce PAs.[1,24] They suggest that even though it is able to induce some anxiety, hyperventilation cannot trigger a reaction similar to spontaneous PAs in PD patients. Experimental evidence suggests that hyperventilation is a significant component of PD, but questions the idea of a putative causal role. It is, however, unquestionable that some PD patients show symptoms related to hyperventilation as also suggested by the evidence of a relationship between the severity of hyperventilation-induced anxiety symptoms

Table 1 Physiologic changes during respiratory challenges

Challenge	pCO_2	Effect
Hyperventilation	↓	• Vasoconstriction and decrease in cerebral blood flow. • Panic attack.
CO_2 inhalation	↑	• Stimulation of chemoreceptors. • Increased ventilation. • Activation of an abnormally sensitive fear network that includes the central nucleus of the amygdala, hippocampus, periaqueductal gray region, and other brainstem areas. • Panic attack.

pCO_2: Partial pressure of CO_2 in the blood.

and gradual decrease in cerebral blood flow in response to hypercapnia-induced alveolar hyperventilation.[3,5]

Stress-induced hyperventilation produces symptoms that people are prone to misinterpret as life-threatening if they are unaware of the consequences of overbreathing.[11] Misinterpretation of these symptoms increases fear and activates the autonomic nervous system resulting in increasing respiratory frequency that will further washout CO_2 and intensify hypocapnic symptoms.[1] Hyperventilation has been considered as a cause, a correlate, and a consequence of panic attacks.[22,26]

Nardi et al.[13] described the clinical features of hyperventilation-induced PAs in PD patients and compared them with their spontaneous PAs and with spontaneous PAs in PD patients not sensitive to the hyperventilation challenge test. Eighty-eight PD patients were submitted to a hyperventilation challenge test. A total of 51.1% (n = 45) PD patients developed a PA after hyperventilating. The clinical symptoms of the most severe PA were recorded by the patients that experienced hyperventilation-induced PAs and by the PD patients not sensitive to this test (non-hyperventilation-induced PA) in a diary during a 1-week period and then compared. The hyperventilation-induced PA group had more frequent and severe respiratory symptoms, fulfilling the criteria for the respiratory PD subtype.[18]

Our group has been studying the relationship between hyperventilation and PA, contrasting PD patients with normal control subjects,[27] with healthy first-degree relatives of the patients,[26] and other anxiety and mood disorders.[25,28,29] In all instances, the PD group presented a higher sensitivity to the hyperventilation challenge test. In a previous study, we submitted PD patients to the hyperventilation challenge test and compared the patients that developed PAs with those that did not present PAs.[13] Patients who panicked during the test had more frequently a family history of mental disorder, older age at the disorder onset, and more frequent previous depressive episodes. The spontaneous and induced PAs were very similar in those subjects that exhibited a PA, but in those individuals that did not develop panic after hyperventilating, the spontaneous PAs were accompanied by a larger amount of chills/hot flushes and much less frequent respiratory symptoms, such as shortness of breath, choking sensation, chest pain/discomfort, paresthesias, and fear of dying.

Although these data seem to support the idea of a causal role of hyperventilation, several pieces of evidence argue against it[1,30-35] and suggest that even though it is able to induce some anxiety, hyperventilation cannot induce a reaction similar to spontaneous PAs in PD patients.[36] Spontaneous PAs, as a rule, are not associated with a decrease in pCO_2 levels,[37-39] and several studies reported the absence of baseline chronic hyperventilation in PD patients.[10,40,41] The studies that did find signs of chronic respiratory alkalosis were inconclusive, as these signs were not documented in more than 50% of the patients.[42-44] If present, chronic hyperventilation seems far from being specific for PD subjects: it was so often found in patients with other anxiety disorders.[35] Finally, many studies[1,32,34] but not all[45] show that hypercapnia is definitely a stronger panicogenic challenge than hyperventilation.

Table 2 Differences between the respiratory subtype and the non-respiratory subtype

Evidence type	RS	NRS	Reference
Familial history of PD	+	-	Freire et al.,[80] Nardi et al.,[76] Nardi et al.[77]
Comorbidity			
With agoraphobia	+	-	Roberson-Nay et al.[75]
With SAD	+	-	Roberson-Nay et al.[75]
With GAD	+	-	Roberson-Nay et al.[75]
With specific phobia	+	-	Roberson-Nay et al.[75]
Scores in PD severity scales			
Clinical Global Impression	+	-	Valença et al.[78]
Anxiety Sensitivity Index	+	-	Onur et al.[74]
Panic-Agoraphobia Spectrum Scale	+	-	Onur et al.[74]
Sensitivity to CO_2 challenge tests			
5% rebreathing challenge	+	-	Abrams et al.[79]
35% single breath challenge	+	-	Biber et al.[19]
35% double-breath challenge	+	-	Freire et al.,[80] Valença et al.,[78] Nardi et al.[83]
Sensitivity to breath holding challenge tests	+	-	Nardi et al.,[81] Nardi et al.[83]
Sensitivity to hyperventilation challenge tests	+	-	Freire et al.,[80] Nardi et al.[81]
Sensitivity to caffeine challenge tests	+	-	Nardi et al.[56]

PD: panic disorder; SAD: social anxiety disorder; GAD: generalized anxiety disorder; RS: respiratory subtype; NRS: non-respiratory subtype.

Carbon dioxide

The CO_2 challenge test strongly suggests a relationship between the pathophysiology of PD and disturbances in the control of breathing.[22] Schruers et al.[46] observed that scanty accurate information is available on the symptomatology of real-life panic attacks and how well they are reproduced by an experimental model such as the 35% CO_2 test. Possibly, research on the association between CO_2 and PD will better characterize subtypes of PD and their underlying mechanisms.

Gorman et al.[31] observed that subjects with PD, in contrast with healthy controls, develop a panic-like reaction within minutes after starting breathing a mixture containing 5% CO_2. CO_2-induced PA is associated with cardiorespiratory activation, including increased respiratory rate and blunted tidal volume response, tachycardia, and increased blood pressure.[11,31,47,48] Sanderson et al.[49] concluded that, despite remarkable methodological differences across various studies, it has been unequivocally established that subjects with PD are hypersensitive to hypercapnic gas mixtures.

A different method of doing CO_2 challenges has also been developed, consisting of one single vital capacity breath of a gas mixture containing 35% CO_2 and 65% oxygen.[50] When given to healthy subjects, this type of challenge results in a brief but strong respiratory stimulation accompanied by neurovegetative symptoms that largely overlap with those reported by panic patients.[51,52] In PD patients the same intervention induces a sharp and transitory rise in anxiety that has been equaled with a real life PA.[50,53,54] Administered in a controlled laboratory environment, the single breath 35% CO_2 challenge constitutes a brief test whose effects are completely vanished in a matter of seconds. Repeated studies have demonstrated that the procedure is safe and devoid of unwanted consequences both in short- and long-term.[55,56] It has been established that CO_2-triggered anxiety is not merely a startle reaction generated by a strong physiological stimulus in overaroused individuals. When administered to a mixed group of patients with various anxiety disorders, all of them with comparable ratings of arousal and anticipatory anxiety, the CO_2 test affected only those with a diagnosis of PD.[57] Specifically, patients with obsessive-compulsive disorder (OCD) failed to show any significant anxiety response to the inhalation of 35% CO_2.[58,59] Similarly, patients with a generalized anxiety disorder (GAD) had little increase in subjective anxiety after a deep breath of CO_2.[60,61] Among patients with a specific phobia, making a clear-cut distinction between animal and situational phobics, the 35% CO_2 challenge did not affect animal phobics, whereas situational phobics presented a CO_2-induced reaction tending to resemble that of PD subjects.[62]

Perna et al.[63] studied dyspnea symptoms during 35% CO_2 inhalations. About a half of the panic disorder patients reported: "I cannot take a deep breath" and "My breath does not go in all the way". The statements: "I feel out of breath", "My breathing requires more concentration" and "My breathing requires effort" were also very common, and more than 35% of the patients reported these symptoms. The symptoms reported were not influenced by gender, age or educational level. The authors performed a factor analysis and identified three factors which accounted for 80% of the variance: "breathing effort", "sense of suffocation" and "rapid breath". The factor "breathing effort" describes the conscious awareness of muscular effort during activation of respiratory skeletal muscles that is thought to arise from dissociation between a central respiratory motor command and a mechanical response of the respiratory muscles. A thoracic breathing pattern and a higher irregularity and instability in baseline breathing patterns which are characteristic of patients with PD, could affect the ability of patients with PD to maintain an adequate respiratory homeostasis when external or internal changes occur. Dissociation between the increased central respiratory command stimulated by CO_2 and a decreased mechanical efficiency of the respiratory response might, therefore, lead to a heightened sense of breathing effort during the CO_2 challenge test. The factor "sense of suffocation" arises mainly from the stimulation of chemoreceptors and involves the activation of the limbic/paralimbic and cerebellar regions. The "rapid breath" factor, which describes a shallow, rapid breathing pattern in response to an excessive mechanical load, was not associated with CO_2 reactivity.

Panicogenicity to CO_2 inhalation increases in the face of serotonin antagonists such as metergoline[64] and tryptophan depletion,[65,66] and decreases with SSRIs.[67-69] These data, together with studies demonstrating blockade of CO_2-panic by benzodiazepines[54] and tricyclic antidepressants,[67] suggest that serotonin, GABA, and noradrenergic neurotransmission play a relevant role in CO_2-induced panic.

The influence of genetics on CO_2-induced panic has also been considered. It was suggested that CO_2 sensitivity reflects a trait marker that runs in families.[55,70,71] According to these researchers, CO_2 sensitivity may be considered a phenotypic expression of an underlying genetic vulnerability that may exist before the clinical onset of PD.[72] The genetic mechanisms proposed include differential expressions of chemoreceptors and neurotransmitter system activation. The ultimate isolation of genetic markers could lead to preventative measures for vulnerable individuals.

CO_2 may represent another safe and effective panicogenic method that has been considered to work primarily by stimulation of hyperventilation. It remains to be understood whether sensitivity to CO_2 and the associated hyperventilation are a characteristic of all normal subjects and PD patients undergoing PAs. It is possible that CO_2 sensitivity relates to a specific subtype of PD, a hypersensitive homeostatic response ("suffocation alarm"), or simply an indirect cause of panic by means of a nonspecific irritation of any chemical and/or mechanical receptors.

The Panic Disorder Respiratory Subtype

There is scientific evidence that a group of "respiratory symptoms" belongs to a distinct PD subtype.[18] Briggs et al.[18] studied the descriptions of the most recent severe PA of 1,108 PD patients and performed an analysis of the main components of the symptoms. The symptoms: fear of dying, chest pain/discomfort, shortness of breath, paresthesias, and sensation of choking defined a distinct group and the absence of these symptoms defined another group. Patients with four or five of these respiratory symptoms during a PA were assigned to the respiratory subtype group, and patients with three or fewer of these symptoms were assigned to the non-respiratory subtype group. The group with prominent

respiratory symptoms suffered more spontaneous PAs, whereas patients in the non-respiratory subtype group had more situational PAs.

Recent studies indicate that respiratory subtype patients may have higher rates of familial history of PD, lower neuroticism scores, and higher scores in severity scales compared to non-respiratory subtype patients.[73,74] Roberson-Nay et al.[75] studied the PD respiratory subtype in an epidemiologic sample (n = 2,294) and in a clinical sample (n = 1,169) and found high temporal stability for the subtype. The authors also found higher comorbidity rates with agoraphobia, social anxiety disorder, generalized anxiety disorder and specific phobia for the respiratory subtype, compared to the non-respiratory subtype.[75] In two studies with small samples,[76,77] it was found correlation between the respiratory subtype and low comorbidity with major depressive disorder, but in the study from Roberson-Nay et al.[75] they found the opposite. There are also conflicting findings regarding the duration of illness.[19,75] High prevalence of respiratory symptoms was found in patients with nocturnal PAs or traumatic suffocation history.[73]

Biber et al.[19] examined the sensitivity to CO_2 in PD patients based on the subtypes approach. PD patients with prominent respiratory symptoms were more sensitive to the CO_2 challenge, had a significantly longer duration of illness, more severe panic and phobic symptoms, and were more likely to be heavier smokers than were PD patients with non-respiratory symptoms. Valença et al.[78] also aimed to assess the sensitivity to CO_2 challenge test in twenty-seven PD subjects classified into respiratory and non-respiratory subtypes. Fifteen of 16 (93.7%) respiratory PD subtype patients and 5 of 11 (43.4%) non-respiratory PD patients had at least one PA during one of two CO_2 challenges. Respiratory subtype patients were also more sensitive to the 5% CO_2 rebreathing challenge than the non-respiratory subtype patients.[79] Using the 35% CO_2 challenge test and the hyperventilation test, Freire et al.[80] compared 117 patients with the respiratory and non-respiratory subtypes of TP. The respiratory group was more responsive to the tests: 80.3% panicked with CO_2 and 53.0% with the hyperventilation test. Only 11.8% of the non-respiratory patients had PA during the carbon dioxide test and 33.3% during the hyperventilation test. These studies indicate that the respiratory subtype group is more sensitive to the CO_2 challenge test and less sensitive to the hyperventilation test, when compared to the non-respiratory subtype group. Other studies also found that most of the PD patients who had PAs during the hyperventilation,[81,82] the breath-holding[81-83] and the caffeine[56] tests met the criteria for the respiratory subtype.

There is evidence that the respiratory and non-respiratory subtypes respond differently to drugs.[18] In an 8-week medication trial, the respiratory subtype patients presented a better improvement with imipramine, while non-respiratory subtype patients responded better to alprazolam.[18] In another study, the respiratory subtype patients had a faster response to treatment with nortriptyline at 8 weeks, compared to the non-respiratory subjects; however, at 52 weeks both groups had improved equally.[76] Clonazepam yielded a similar behavior in the respiratory PD, i.e., a faster improvement of the symptoms in the beginning of the treatment and a response similar to that of the non-respiratory subtype on the long run.[77] Mavissakalian[84] found that respiratory symptoms, particularly choking, dyspnea and fear, improved significantly at four weeks of treatment with imipramine, whereas other symptoms took longer to improve. Respiratory and non-respiratory subtype patients improved in a similar way with cognitive-behavioral therapy.[73]

Current Mechanistic Concepts

Increased CO_2 sensitivity

There are two lines of evidence suggesting that PAs may originate in the brainstem.[3] The first one advances that the nature of the symptoms can be explained by a surge of impulses from the autonomic nervous system. The second line of evidence is the CO_2-mediated experimental provocation of PA itself. CO_2 primarily acts on the brainstem, especially on the respiratory center, located in the reticular substance of the medulla oblongata and the pons.[3,5] Considering the hyperoxic mixtures that are used in the CO_2 challenges, any stimulating influence of the peripheral oxygen chemosensitive areas is discarded. A number of studies were directed towards a possible dysfunction at the level of the central chemosensitive regions.

To explore CO_2 chemosensitivity in PD patients, the ventilatory response to increasing CO_2 concentration was monitored under the hypothesis that an exaggerated response would confirm oversensitivity. Studies on the ventilatory response to CO_2, i.e., the increase in ventilation due to the inhalation of increasing concentrations of CO_2, yielded contradictory results (Gorman et al.[3]). This may be in part explained by a possible lack of control of confounding variables and the well-known wide inter-individual variability of CO_2 chemosensitivity. Klein[4] proposed that PA results from the deregulation of a phylogenetically evolved alarm system directed to monitor suffocation signals in the organism. This alarm system has been evolutionarily programmed to fire when it senses metabolic signs of asphyxia and impending death. As a survival alert system, this physiologic suffocation monitor most likely has a deeply rooted adaptive function: its activation only occurs in extreme life threatening circumstances. The Klein's hypothesis may help to understand the preeminence of respiratory symptoms in PAs. For example, it may be useful to explain why patients with PD, in contrast with other types of anxiety, against any medical evidence, and despite repeated reassurance, invariably feel an overwhelming fear of dying and losing control during their attacks. Klein points to the existence of the congenital central hypoventilation syndrome.[85] This rare condition affects infants that apparently are born with an aberrant sensitivity to signals of hypercapnia and hypoxia. The congenital hypoventilation syndrome may be the pathophysiological mirror picture of PD.[85]

A drawback of Klein's hypothesis rests on the fact that no suffocation alarm system has been anatomically or functionally identified as such within the central nervous system (CNS). The search for a panic circuitry in the brain should include those areas of the CNS linked to chemosensitive properties. These structures should logically be considered as the best candidates to fulfill the function of a suffocation detector. A few findings support the idea that the CNS chemosensitive areas related to panic responses extend to several

brainstem nuclei, including the nucleus tractus solitarius, the locus coeruleus, and the raphe nuclei, being all these structures part of a broad brainstem respiratory network.[3,5]

Exaggerated cerebrovascular responses to hypocapnia

PD patients experiencing recurrent PAs may display an abnormal cerebrovascular response to alkalosis and be vulnerable to brain hypoxia during hyperventilation.[22] The intermittent hypoxia may disrupt homeostatic mechanisms and neuronal and glial viability within particular brain regions. Subsequent dysfunction of prefrontal cortex (PFC) regions, expressed by dysfunction of a multifaceted cognitive executive system, may alter the functional recruitment of more primary cognitive abilities, resulting in maladaptive behaviors.[86] In clinical practice, it is usual to find patients with a high level of dependence, a constant sense of insecurity, lack of a well-developed capacity for autonomous action, and pathological reassurance sensitivity.

Changes of the central rhythm generator

Breathing pattern at rest may reveal some changes in ventilatory control. Accordingly, several studies investigated PD subjects focusing on baseline respiratory physiology in the intervals between Pas.[31,87,88] However, caution is needed when interpreting these results, as several measurements were obtained immediately before panicogenic challenges, and procedures used to obtain these data are heterogeneous. Most of the studies performed so far failed to find significant differences in mean values of respiratory rate, tidal volume, minute ventilation and respiratory blood gases among patients with PD, healthy controls, or patients with other anxiety disorders.[22] The two main positive findings that have been reproduced are: 1) patients with PD have a thoracic pattern of breathing[89] with a strong muscular thoracic effort; 2) patients with PD show an abnormal variability and irregularity in breathing both during daytime[11,48,90,91] and during sleep.[87]

Other interesting findings are the hematologic alterations found in patients with chronic obstructive pulmonary disease and high altitude dwellers which were also found in PD patients.[92] Ross et al.[92] found that male PD patients, particularly those sensitive to CO_2 inhalations, had elevated mean corpuscular hemoglobin. This finding indicates that compensatory mechanisms to hypoxia may be activated in PD patients.

Because respiration is a complex physiologic function with multiple central and peripheral inputs, its pathophysiological characteristics could be more accurately investigated by the analysis of the complexity of the respiratory recorded signals rather than by a simple measurement of the absolute values of a few parameters. Patients with PD show a larger breath-to-breath variability during a rebreathing test than is usually observed in controls.[93] Compared with healthy subjects, PD patients show an increased irregularity in tidal volume and minute ventilation and an increased rate of apneas during sleep.[87,94] In PD patients, baseline respiratory frequency and tidal volume were found to be more irregular than in healthy controls.[31,48,90] Additionally, PD patients showed excessive sighing and tidal volume irregularity significantly greater than those in healthy control subjects[95,96] and GAD patients.[97] The tidal volume irregularity persisted after both doxapram-induced hyperventilation and cognitive intervention, suggesting that it might be an intrinsic and stable feature of patients with PD.[97] The importance of this finding for the understanding of panic etiopathogenesis is supported by the evidence of a higher variability in respiratory pattern in response to 5% CO_2 inhalation in relatives of PD patients compared to relatives of healthy controls and of affective patients.[98] In this connection, Perna et al.[99] suggested that the variability in respiration might be higher in children of patients with PD than in those born to healthy controls. Two trials[100,101] reported more irregularities in respiratory rate in children with childhood anxiety disorders that developed panic symptoms after CO_2 inhalation. Respiratory irregularities and pattern variability could be a physiological trait marker of panic vulnerability able to identify subjects at risk for PD and promote formal and molecular genetic studies in PD. Normal respiration is characterized by a synchronized action of inspiratory and expiratory neurons and, thus, the high variability observed, together with the unpleasant respiratory sensations that ensue in patients with PD, could be the results of a mismatch of the activity of inspiratory and expiratory neurons. The abnormal responses to respiratory challenges might be the expression of a deranged adaptation mechanism related to this deregulation.[6,22]

Dysfunctional opioid system

The opioid system participates in breathing regulation and social-affiliative behavior explaining the associations between separation anxiety disorder (SAD), CO_2 and lactate sensitivity, other respiratory phenomena, and PD.[102] In the extended version of the false suffocation alarm theory, an episodic dysfunction in the endogenous opioide system regulation explains the false alarms in PD patients.[102] SAD patients have high incidence of PD[103] and familial history of PD.[104] Roberson-Nay et al.[105] found that subjects with both SAD and at least one parent with PD were more sensitive to CO_2. The risk of a PA in these patients during a 5% CO_2 inhalation was threefold higher compared to subjects without SAD or familial history of PD. This finding indicates that SAD combined with familial history of PD may increase the risk of PD.[105]

The endogenous opioid system was recognized as an important central regulator of respiratory drive[106] and, when the opioid receptors are stimulated, CO_2 sensitivity reduces and respiratory rate slows down.[107] Also, the administration of codeine allows high levels of carbon dioxide to be tolerated during breath holding.[108] Conversely, naloxone, an opioid receptor antagonist, increases the ventilatory response to hypercapnic hypoxia in normal human subjects.[109] Recent studies[110-112] indicate that naloxone increases the respiratory response to lactate in healthy subjects. In the study by Preter et al.[111] sodium lactate was administered intravenously to 25 healthy subjects who received a pretreatment with naloxone or saline. The administration of naloxone or saline was randomized and crossed-over, in two different days. Compared to the saline group, the naloxone group had higher tidal volume, respiratory rate and minute ventilation, but there were no differences regarding panic symptoms and subjective breathlessness. Among subjects pretreated with naloxone, those with childhood parental loss (parental death or divorce

before the age of 10) showed milder increase in ventilatory parameters, compared to those without childhood parental loss.[111] These findings indicate that the susceptibility of panic disorder patients to lactate-induced panic may imply a deregulation of the opioid system.[110,111]

Neurobiological changes

A recent model of PD attempts to integrate neurochemical, imaging, and treatment findings, coupled with mostly preclinical work, in the neurobiology of conditioned fear responses.[3,113] The PA is speculated to originate in 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, then to the central nucleus of the amygdala, where all the information is gathered and the autonomic and behavioral responses are coordinated. The CNA sends stimuli to the parabrachial nucleus, increasing respiration rate;[114] the lateral nucleus of the hypothalamus, activating the sympathetic nervous system; the locus ceruleus, increasing the norepinephrine release and contributing to increases in blood pressure, heart rate and the behavioral fear response; and the paraventricular nucleus of the hypothalamus, causing an increase in the release of adrenocorticoids. A projection from the CNA to the periaqueductal grey region is responsible for additional behavioral responses, including defensive behaviors and postural freezing. There are also important reciprocal connections between the amygdala and sensory thalamus, prefrontal cortex, insula and primary somatosensory cortex. Although the amygdala receives direct sensory input from brainstem structures and the sensory thalamus, enabling a rapid response to potentially threatening stimuli, it also receives afferents from cortical regions involved in processing and evaluation of sensory information. A neurocognitive deficit could result in a misinterpretation of sensory information, leading to an 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 brainstem could lead to an abnormal activation of the amygdala, with a behavioral, autonomic and neuroendocrine activation. Panic originates in an abnormally sensitive fear network, which includes the prefrontal cortex, insula, thalamus, amygdala and amygdalar projections to the brainstem and hypothalamus.[3,113]

The potential role of hypoxia as a signal of asphyxia and the suggested sensitivity of PD patients to anoxia are supported by evidences from animal studies reporting that the amygdala and the hippocampus are particularly sensitive to anoxic stimulation. Together with the evidence of strong connections between the amygdala and the carotid body, the direct sensitivity of amygdala to acid-base changes, and the interconnections between the amygdala and the parabrachial nucleus[114] may delineate another pathway linking respiratory signals to panic.[115]

Conclusion

There is a substantial body of literature demonstrating that stimulation of respiration is a common event in PD patients during a PA. A number of changes in respiration, such as enhanced CO_2 sensitivity, have been detected in PD patients. As a result, some investigators advanced that there is a fundamental abnormality in the physiological mechanisms that control breathing in PD. Accumulated evidence suggests that the respiratory physiology remains normal in PD patients and that their tendency to hyperventilate and react with panic to respiratory stimulants like CO_2 represents the triggering of a hypersensitive fear network. However, some recent evidences support the presence of subclinical abnormalities in respiration and other functions related to body homeostasis. Hence, the role of a more primitive and lower brain center than the limbic one should be considered. To date, the fear network has been investigated in preclinical studies that have identified the brain pathways that promote the acquisition and maintenance of conditioned fear. The amygdala and its brain stem projections, the hippocampus, and the medial prefrontal cortex operate in this network. Although attempts to image this system in patients during panic attacks have been so far inconclusive, the theory that the fear network is operative and hyperactive in PD patients might explain why both medication and psychosocial therapies are clearly effective. Although to date it is not clear if the abnormal function underlying PAs lies in the limbic system, mainly related to fear, or in the brainstem, mainly related to a primitive emotion, one cannot forget the complex relationships between these two brain areas. Therefore, the whole picture of PD should be viewed as the complex result of multiple interactions between various brain networks. The evidence of abnormalities in several neurochemical systems might be just the expression of the complex interaction among brain circuits. Hence, the attempt to focus on one isolated component of this complex array as the "pathogenetic" system of PD seems unwarranted.

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Rafael C. Freire
Employment: *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro, National Institute for Translational Medicine (INCT-TM), Rio de Janeiro, Brazil.* ***Research grant:*** *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes), Brazil.*

Antonio E. Nardi
Employment: *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro, National Institute for Translational Medicine (INCT-TM), Rio de Janeiro, Brazil.* **Research grant:** *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes), Brazil.*

References

1. Gorman JM, Papp LA, Coplan JD, Martinez JM, Lennon S, Goetz RR et al. Anxiogenic effects of CO2 and hyperventilation in patients with panic disorder. Am J Psychiatry. 1994;151(4):547-53.

2. Papp LA, Schneier FR, Fyer AJ, Leibowitz MR, Gorman JM, Coplan JD et al. Clomipramine treatment of panic disorder: pros and cons. J Clin Psychiatry. 1997;58(10):423-5.
3. Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry. 2000;157(4):493-505.
4. Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. Arch Gen Psychiatry. 1993;50(4):306-17.
5. Griez E, Perna G. Respiration and Anxiety. In: Nutt D, Ballenger J, editors. Anxiety Disorder.Oxford: Blackwell Science Ltd.; 2003. pp. 251-67.
6. Perna G, Caldirola D, Bellodi L. Panic disorder: from respiration to the homeostatic brain. Acta Neuropsychiatrica. 2004;16:57-67.
7. Papp LA, Klein DF, Gorman JM. Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. Am J Psychiatry. 1993;150(8):1149-57.
8. Battaglia M, Perna G. The 35% CO2 challenge in panic disorder: optimization by receiver operating characteristic (ROC) analysis. J Psychiatr Res. 1995;29(2):111-9.
9. Rapee RM, Sanderson WC, McCauley PA, Di Nardo PA. Differences in reported symptom profile between panic disorder and other DSM-III-R anxiety disorders. Behav Res Ther. 1992;30(1):45-52.
10. Holt PE, Andrews G. Hyperventilation and anxiety in panic disorder, social phobia, GAD and normal controls. Behav Res Ther. 1989;27(4):453-60.
11. Papp LA, Martinez JM, Klein DF, Coplan JD, Norman RG, Cole R et al. Respiratory psychophysiology of panic disorder: three respiratory challenges in 98 subjects. Am J Psychiatry. 1997;154(11):1557-65.
12. Dorow R, Horowski R, Paschelke G, Amin M. Severe anxiety induced by FG 7142, a beta-carboline ligand for benzodiazepine receptors. Lancet. 1983;2(8341):98-9.
13. Nardi AE, Lopes FL, Valenca AM, Nascimento I, Mezzasalma MA, Zin WA. Psychopathological description of hyperventilation-induced panic attacks: a comparison with spontaneous panic attacks. Psychopathology. 2004;37(1):29-35.
14. Nardi AE, Nascimento I, Valenca AM, Lopes FL, Mezzasalma MA, Zin WA. Panic disorder in a breath-holding challenge test: a simple tool for a better diagnosis. Arq Neuropsiquiatr. 2003;61(3B):718-22.
15. Little HJ, Nutt DJ, Taylor SC. Bidirectional effects of chronic treatment with agonists and inverse agonists at the benzodiazepine receptor. Brain Res Bull. 1987;19(3):371-8.
16. Nutt D, Lawson C. Panic attacks. A neurochemical overview of models and mechanisms. Br J Psychiatry. 1992;160:165-78.
17. Malizia AL, Gunn RN, Wilson SJ, Waters SH, Bloomfield PM, Cunningham VJ et al. Benzodiazepine site pharmacokinetic/pharmacodynamic quantification in man: direct measurement of drug occupancy and effects on the human brain in vivo. Neuropharmacology 1996;35(9-10):1483-91.
18. Briggs AC, Stretch DD, Brandon S. Subtyping of panic disorder by symptom profile. Br J Psychiatry. 1993;163:201-9.
19. Biber B, Alkin T. Panic disorder subtypes: Differential responses to CO2 challenge. Am J Psychiatry. 1999;156(5):739-44.
20. Garssen B, van VW, Bloemink R. Agoraphobia and the hyperventilation syndrome. Behav Res Ther. 1983;21(6):643-9.
21. Cowley DS, Roy-Byrne PP. Hyperventilation and panic disorder. Am J Med. 1987;83(5):929-37.
22. Bellodi L, Perna G. The Panic Respiration Connection. Milan: MDM Medical Media; 1998.
23. Anderson DJ, Noyes R, Jr., Crowe RR. A comparison of panic disorder and generalized anxiety disorder. Am J Psychiatry. 1984;141(4):572-5.
24. Ley R. Agoraphobia, the panic attack and the hyperventilation syndrome. Behav Res Ther. 1985;23(1):79-81.
25. Nardi AE, Valenca AM, Nascimento I, Zin WA. Hyperventilation challenge test in panic disorder and depression with panic attacks. Psychiatry Res. 2001 15;105(1-2):57-65.
26. Nardi AE, Valenca AM, Nascimento I, Mezzasalma MA, Lopes FL, Zin WA. Hyperventilation in panic disorder patients and healthy first-degree relatives. Braz J Med Biol Res. 2000;33(11):1317-23.
27. Nardi AE, Valenca AM, Nascimento I, Mezzasalma MA, Zin W. Panic disorder and hyperventilation. Arq Neuropsiquiatr. 1999;57(4):932-6.
28. Nardi AE, Valenca AM, Nascimento I, Zin WA. Panic disorder and obsessive compulsive disorder in a hyperventilation challenge test. J Affect Disord. 2002;68(2-3):335-40.
29. Nardi AE, Valenca AM, Nascimento I, Mezzasalma MA, Zin WA. Hyperventilation in panic disorder and social phobia. Psychopathology. 2001;34(3):123-7.
30. Gorman JM, Askanazi J, Liebowitz MR, Fyer AJ, Stein J, Kinney JM et al. Response to hyperventilation in a group of patients with panic disorder. Am J Psychiatry. 1984;141(7):857-61.
31. Gorman JM, Fyer MR, Goetz R, Askanazi J, Liebowitz MR, Fyer AJ et al. Ventilatory physiology of patients with panic disorder. Arch Gen Psychiatry. 1988;45(1):31-9.
32. Zandbergen J, Lousberg HH, Pols H, de LC, Griez EJ. Hypercarbia versus hypocarbia in panic disorder. J Affect Disord. 1990;18(2):75-81.
33. Asmundson GJG, Stein MB. A Preliminary-Analysis of Pulmonary-Function in Panic Disorder - Implications for the Dyspnea-Fear Theory. J Anxiety Disord. 1994;8(1):63-9.
34. Antony MM, Brown TA, Barlow DH. Response to hyperventilation and 5.5% CO2 inhalation of subjects with types of specific phobia, panic disorder, or no mental disorder. Am J Psychiatry. 1997;154(8):1089-95.
35. Van den Hout MA, Hoekstra R, Arntz A, Christiaanse M, Ranschaert W, Schouten E. Hyperventilation is not diagnostically specific to panic patients. Psychosom Med. 1992;54(2):182-91.
36. Lindsay S, Saqi S, Bass C. The test-retest reliability of the hyperventilation provocation test. J Psychosom Res. 1991;35(2-3):155-62.
37. Hibbert G, Pilsbury D. Hyperventilation in panic attacks. Ambulant monitoring of transcutaneous carbon dioxide. Br J Psychiatry. 1988;153:76-80.
38. Hibbert G, Pilsbury D. Hyperventilation: is it a cause of panic attacks? Br J Psychiatry. 1989;155:805-9.
39. Buikhuisen M, Garssen B. Hyperventilation and panic attacks. Biol Psychol. 1990;31:280.
40. Woods SW, Charney DS, Loke J, Goodman WK, Redmond DE, Jr., Heninger GR. Carbon dioxide sensitivity in panic anxiety. Ventilatory and anxiogenic response to carbon dioxide in healthy subjects and patients with panic anxiety before and after alprazolam treatment. Arch Gen Psychiatry. 1986;43(9):900-9.
41. Zandbergen J, van Aalst V, de Loof C, Pols H, Griez E. No chronic hyperventilation in panic disorder patients. Psychiatry Res. 1993;47(1):1-6.
42. Liebowitz MR, Gorman JM, Fyer AJ, Levitt M, Dillon D, Levy G et al. Lactate provocation of panic attacks. II. Biochemical and physiological findings. Arch Gen Psychiatry. 1985;42(7):709-19.
43. Gorman JM, Liebowitz MR, Fyer AJ, Fyer MR, Klein DF. Possible respiratory abnormalities in panic disorder. Psychopharmacol Bull. 1986;22(3):797-801.
44. Salkovskis PM, Warwick HM, Clark DM, Wessels DJ. A demonstration of acute hyperventilation during naturally occurring panic attacks. Behav Res Ther. 1986;24(1):91-4.

45. Schmidt NB, Telch MJ, Jaimez TL. Biological challenge manipulation of PCO2 levels: a test of Klein's (1993) suffocation alarm theory of panic. J Abnorm Psychol. 1996;105(3):446-54.
46. Schruers KRJ, van de Mortel H, Overbeek T, Griez E. Symptom profiles of natural and laboratory panic attacks. Acta Neuropsychiatrica. 2004;16(2):101-6.
47 Bailey JE, Argyropoulos SV, Kendrick AH, Nash J, Jightman S, Nutt DJ. Inhalation of 35% CO2 results in subjective fear and activates the HPA axis in healthy volunteers. J Psychopharmacol. 2001;15:A22.
48. Bystritsky A, Craske M, Maidenberg E, Vapnik T, Shapiro D. Autonomic reactivity of panic patients during a CO2 inhalation procedure. Depress Anxiety. 2000;11(1):15-26.
49. Sanderson WC, Wetzler S. Five percent carbon dioxide challenge: valid analogue and marker of panic disorder? Biol Psychiatry. 1990 1;27(7):689-701.
50. Griez EJ, Lousberg H, Van den Hout MA, van der Molen GM. CO2 vulnerability in panic disorder. Psychiatry Res. 1987;20(2):87-95.
51. Griez E, Van den Hout MA. Effects of carbon dioxide-oxygen inhalations on subjective anxiety and some neurovegetative parameters. J Behav Ther Exp Psychiatry. 1982;13(1):27-32.
52. Van den Hout MA, Griez E. Panic symptoms after inhalation of carbon dioxide. Br J Psychiatry. 1984;144:503-7.
53. Perna G, Battaglia M, Garberi A, Arancio C, Bertani A, Bellodi L. Carbon-Dioxide Oxygen Challenge Test in Panic Disorder. Psychiatry Res. 1994;52(2):159-71.
54. Nardi AE, Valenca AM, Nascimento I, Mezzasalma MA, Zin WA. Double-blind acute clonazepam vs. placebo in carbon dioxide-induced panic attacks. Psychiatry Res. 2000;94(2):179-84.
55. Perna G, Cocchi S, Allevi L, Bussi R, Bellodi L. A long-term prospective evaluation of first-degree relatives of panic patients who underwent the 35% CO2 challenge. Biol Psychiatry. 1999;45(3):365-7.
56. Nardi AE, Valenca AM, Lopes FL, De-Melo-Neto VL, Freire RC, Veras AB et al. Caffeine and 35% carbon dioxide challenge tests in panic disorder. Hum Psychopharmacol. 2007;22(4):231-40.
57. Griez E, Zandbergen J, Pols H, de LC. Response to 35% CO2 as a marker of panic in severe anxiety. Am J Psychiatry. 1990;147(6):796-7.
58. Griez E, de Loof C, Pols H, Zandbergen J, Lousberg H. Specific sensitivity of patients with panic attacks to carbon dioxide inhalation. Psychiatry Res. 1990;31(2):193-9.
59. Perna G, Bertani A, Arancio C, Ronchi P, Bellodi L. Laboratory response of patients with panic and obsessive-compulsive disorders to 35% CO2 challenges. Am J Psychiatry. 1995;152(1):85-9.
60. Perna G, Bussi R, Allevi L, Bellodi L. Sensitivity to 35% carbon dioxide in patients with generalized anxiety disorder. J Clin Psychiatry. 1999;60(6):379-84.
61. Verburg K, Griez E, Meijer J, Pols H. Discrimination between panic disorder and generalized anxiety disorder by 35% carbon dioxide challenge. Am J Psychiatry. 1995;152(7):1081-3.
62. Verburg C, Griez E, Meijer J. A 35% carbon dioxide challenge in simple phobias. Acta Psychiatr Scand. 1994;90(6):420-3.
63. Perna G, Caldirola D, Namia C, Cucchi M, Vanni G, Bellodi L. Language of dyspnea in panic disorder. Depress Anxiety. 2004;20(1):32-8.
64. Ben-Zion IZ, Meiri G, Greenberg BD, Murphy DL, Benjamin J. Enhancement of CO2-induced anxiety in healthy volunteers with the serotonin antagonist metergoline. Am J Psychiatry. 1999;156(10):1635-7.
65. Miller HE, Deakin JF, Anderson IM. Effect of acute tryptophan depletion on CO2-induced anxiety in patients with panic disorder and normal volunteers. Br J Psychiatry. 2000;176:182-8.
66. Schruers K, Klaassen T, Pols H, Overbeek T, Deutz NE, Griez E. Effects of tryptophan depletion on carbon dioxide provoked panic in panic disorder patients. Psychiatry Res. 2000;93(3):179-87.
67. Bertani A, Perna G, Arancio C, Caldirola D, Bellodi L. Pharmacologic effect of imipramine, paroxetine, and sertraline on 35% carbon dioxide hypersensitivity in panic patients: a double-blind, random, placebo-controlled study. J Clin Psychopharmacol. 1997;17(2):97-101.
68. Pols HJ, Hauzer RC, Meijer JA, Verburg K, Griez EJ. Fluvoxamine attenuates panic induced by 35% CO2 challenge. J Clin Psychiatry. 1996;57(11):539-42.
69. Perna G, Bertani A, Gabriele A, Politi E, Bellodi L. Modification of 35% carbon dioxide hypersensitivity across one week of treatment with clomipramine and fluvoxamine: a double-blind, randomized, placebo-controlled study. J Clin Psychopharmacol. 1997;17(3):173-8.
70. Perna G, Cocchi S, Bertani A, Arancio C, Bellodi L. Sensitivity to 35% CO2 in healthy first-degree relatives of patients with panic disorder. Am J Psychiatry. 1995;152(4):623-5.
71 Bellodi L, Perna G, Caldirola D, Arancio C, Bertani A, Di BD. CO2-induced panic attacks: a twin study. Am J Psychiatry. 1998;155(9):1184-8.
72. Cavallini MC, Perna G, Caldirola D, Bellodi L. A segregation study of panic disorder in families of panic patients responsive to the 35% CO2 challenge. Biol Psychiatry. 1999;46(6):815-20.
73. Freire RC, Perna G, Nardi AE. Panic Disorder Respiratory Subtype: Psychopathology, Laboratory Challenge Tests, and Response to Treatment. Harv Rev Psychiatry. 2010;18(4):220-9.
74. Onur E, Alkin T, Tural U. Panic disorder subtypes: Further clinical differences. Depress Anxiety. 2007;24(7):479-86.
75. Roberson-Nay R, Latendresse SJ, Kendler KS. A latent class approach to the external validation of respiratory and non-respiratory panic subtypes. Psychol Med. 2012;42(3):461-74.
76. Nardi AE, Nascimento I, Valenca AM, Lopes FL, Mezzasalma MA, Zin WA et al. Respiratory panic disorder subtype: acute and long-term response to nortriptyline, a noradrenergic tricyclic antidepressant. Psychiatry Res. 2003;120(3):283-93.
77. Nardi AE, Valenca AM, Nascimento I, Lopes FL, Mezzasalma MA, Freire RC et al. A three-year follow-up study of patients with the respiratory subtype of panic disorder after treatment with clonazepam. Psychiatry Res. 2005;137(1-2):61-70.
78. Valença AM, Nardi AE, Nascimento I, Zin WA, Versiani M. Respiratory panic disorder subtype and sensitivity to the carbon dioxide challenge test. Braz J Med Bio Res. 2002;35(7):783-8.
79. Abrams K, Rassovsky Y, Kushner MG. Evidence for respiratory and nonrespiratory subtypes in panic disorder. Depress Anxiety 2006;23(8):474-81.
80. Freire RC, Lopes FL, Valenca AM, Nascimento I, Veras AB, Mezzasalma MA et al. Panic disorder respiratory subtype: A comparison between responses to hyperventilation and CO(2) challenge tests. Psychiatry Res. 2008;157(1-3):307-10.
81. Nardi AE, Valenca AM, Lopes FL, Nascimento I, Mezzasalma MA, Zin WA. Clinical features of panic patients sensitive to hyperventilation or breath-holding methods for inducing panic attacks. Braz J Med Bio Res. 2004;37(2):251-7.
82. Nardi AE, Valenca AM, Mezzasalma MA, Levy SP, Lopes FL, Nascimento I et al. Comparison between hyperventilation and breath-holding in panic disorder: Patients responsive and non-responsive to both tests. Psychiatry Res. 2006;142(2-3):201-8.
83. Nardi AE, Valenca AM, Mezzasalma MA, Lopes FL, Nascimento I, Veras AB et al. 35% carbon dioxide and breath-holding challenge tests in panic disorder: A comparison with spontaneous panic attacks. Depress Anxiety 2006;23(4):236-44.

84. Mavissakalian MR. Phenomenology of panic attacks: Responsiveness of individual symptoms to imipramine. J Clin Psychopharmacol. 1996;16(3):233-7.
85. Pine DS, Weese-Mayer DE, Silvestri JM, Davies M, Whitaker AH, Klein DF. Anxiety and congenital central hypoventilation syndrome. Am J Psychiatry. 1994;151(6):864-70.
86. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11(1):1-16.
87. Stein MB, Millar TW, Larsen DK, Kryger MH. Irregular breathing during sleep in patients with panic disorder. Am J Psychiatry. 1995;152(8):1168-73.
88. Caldirola D, Bellodi L, Caumo A, Migliarese G, Perna G. Approximate entropy of respiratory patterns in panic disorder. Am J Psychiatry. 2004;161(1):79-87.
89. Beck JG, Scott SK. Physiological and symptom responses to hyperventilation: a comparison of frequent and infrequent panickers. J Psychopathol Behav Assess. 1988;10:117-27.
90. Bystritsky A, Shapiro D. Continuous physiological changes and subjective reports in panic patients: a preliminary methodological report. Biol Psychiatry 1992 Nov 1;32(9):766-77.
91. Schwartz GE, Goetz RR, Klein DF, Endicott J, Gorman JM. Tidal volume of respiration and "sighing" as indicators of breathing irregularities in panic disorder patients. Anxiety. 1996;2(3):145-8.
92. Ross DC, Preter M, Klein DF. Hematologic alterations and CO(2) hypersensitivity in male panic disorder patients and normal controls: similarities to high-altitude hypoxia and chronic lung disease. Depress Anxiety. 2001;14(2):153-4.
93. Papp LA, Martinez JM, Klein DF, Coplan JD, Gorman JM. Rebreathing tests in panic disorder. Biol Psychiatry. 1995;38(4):240-5.
94. Martinez JM, Papp LA, Coplan JD, Anderson DE, Mueller CM, Klein DF, Gorman JM. Ambulatory monitoring of respiration in anxiety. Anxiety. 1996;2(6):296-302.
95. Abelson JL, Weg JG, Curtis GC. Respiratory irregularity in panic patients may reflect excessive sighing. Biol Psychiatry. 2000;47(Suppl.1):157-8.
96. Abelson JL, Weg JG, Nesse RM, Curtis GC. Persistent respiratory irregularity in patients with panic disorder. Biol Psychiatry. 2001;49(7):588-95.
97. Wilhelm FH, Trabert W, Roth WT. Physiologic instability in panic disorder and generalized anxiety disorder. Biological Psychiatry. 2001;49(7):596-605.
98. Coryell W, Fyer A, Pine D, Martinez J, Arndt S. Aberrant respiratory sensitivity to CO(2) as a trait of familial panic disorder. Biol Psychiatry. 2001 Apr 1;49(7):582-7.
99. Perna G, Ieva A, Caldirola D, Bertani A, Bellodi L. Respiration in children at risk for panic disorder. Arch Gen Psychiatry. 2002;59(2):185-6.
100. Pine DS, Coplan JD, Papp LA, Klein RG, Martinez JM, Kovalenko P, Tancer N, Moreau rD, Dummit ES 3rd, Shaffer D, Klein DF, Gorman JM. Ventilatory physiology of children and adolescents with anxiety disorders. Arch Gen Psychiatry. 1998;55(2):123-9.
101. Pine DS, Klein RG, Coplan JD, Papp LA, Hoven CW, Martinez J, Kovalenkro P, Mandell rDJ, Moreau D, Klein DF, Gorman JM. Differential carbon dioxide sensitivity in childhood anxiety disorders and nonill comparison group. Arch Gen Psychiatry. 2000;57(10):960-7.
102. Preter M, Klein DF. Panic, suffocation false alarms, separation anxiety and endogenous opioids. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(3):603-12.
103. Klein RG. Is panic disorder associated with childhood separation anxiety disorder. Clin Neuropsychopharmacology. 1995;18(Suppl 2):7-14.
104. Battaglia M, Bertella S, Politi E, Bernardeschi L, Perna G, Gabriele A et al. Age at onset of panic disorder: influence of familial liability to the disease and of childhood separation anxiety disorder. Am J Psychiatry. 1995;152(9):1362-4.
105. Roberson-Nay R, Klein DF, Klein RG, Mannuzza S, Moulton JL, III, Guardino M, Pine DS. Carbon dioxide hypersensitivity in separation-anxious offspring of parents with panic disorder. Biol Psychiatry. 2010;67(12):1171-7.
106. Akil H, Watson SJ, Young E, Lewis ME, Khachaturian H, Walker JM. Endogenous opioids: biology and function. Annu Rev Neurosci. 1984;7:223-55.
107. Fleetham JA, Clarke H, Dhingra S, Chernick V, Anthonisen NR. Endogenous opiates and chemical control of breathing in humans. Am Rev Respir Dis. 1980;121(6):1045-9.
108. Stark RD, Morton PB, Sharman P, Percival PG, Lewis JA. Effects of codeine on the respiratory responses to exercise in healthy subjects. Br J Clin Pharmacol. 1983;15(3):355-9.
109. Akiyama Y, Nishimura M, Kobayashi S, Yoshioka A, Yamamoto M, Miyamoto K et al. Effects of naloxone on the sensation of dyspnea during acute respiratory stress in normal adults. J Appl Physiol 1993;74(2):590-5.
110. Sinha SS, Goetz RR, Klein DF. Physiological and behavioral effects of naloxone and lactate in normal volunteers with relevance to the pathophysiology of panic disorder. Psychiatry Res. 2007;149(1-3):309-14.
111. Preter M, Lee SH, Petkova E, Vannucci M, Kim S, Klein DF. Controlled cross-over study in normal subjects of naloxone-preceding-lactate infusions; respiratory and subjective responses: relationship to endogenous opioid system, suffocation false alarm theory and childhood parental loss. Psychol Med. 2011;41(2):385-93.
112. Lee SH, Lim J, Vannucci M, Petkova E, Preter M, Klein DF. Order-preserving dimension reduction procedure for the dominance of two mean curves with application to tidal volume curves. Biometrics. 2008;64(3):931-9.
113. Mezzasalma MA, Valenca AM, Lopes FL, Nascimento I, Zin WA, Nardi AE. Neuroanatomy of panic disorder. Rev Bras Psiquiatr. 2004;26(3):202-6.
114. Takeuchi Y, McLean JH, Hopkins DA. Reciprocal connections between the amygdala and parabrachial nuclei: ultrastructural demonstration by degeneration and axonal transport of horseradish peroxidase in the cat. Brain Res. 1982;239(2):583-8.
115. Coplan JD, Lydiard RB. Brain circuits in panic disorder. Biol Psychiatry. 1998;44(12):1264-76.