The role of hyperventilation - hypocapnia in the pathomechanism of panic disorder

O papel da hiperventilação - a hipocapnia no patomecanismo do distúrbio de pânico

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Abstract

Objective: *The authors present a profile of panic disorder based on and generalized from the effects of acute and chronic hyperventilation that are characteristic of the respiratory panic disorder subtype. The review presented attempts to integrate three premises: hyperventilation is a physiological response to hypercapnia; hyperventilation can induce panic attacks; chronic hyperventilation is a protective mechanism against panic attacks.* *Method*: *A selective review of the literature was made using the Medline database. Reports of the interrelationships among panic disorder, hyperventilation, acidosis, and alkalosis, as well as catecholamine release and sensitivity, were selected. The findings were structured into an integrated model.* *Discussion*: *The panic attacks experienced by individuals with panic disorder develop on the basis of metabolic acidosis, which is a compensatory response to chronic hyperventilation. The attacks are triggered by a sudden increase in (pCO_2) when the latent (metabolic) acidosis manifests as hypercapnic acidosis. The acidotic condition induces catecholamine release. Sympathicotonia cannot arise during the hypercapnic phase, since low pH decreases catecholamine sensitivity. Catecholamines can provoke panic when hyperventilation causes the hypercapnia to switch to hypocapnic alkalosis (overcompensation) and catecholamine sensitivity begins to increase.* *Conclusion*: *Therapeutic approaches should address long-term regulation of the respiratory pattern and elimination of metabolic acidosis.*

Descriptors: *Acidosis; Catecholamines; Hyperventilation; Hypocapnia; Panic disorder*

Resumo

Objetivo: *Os autores apresentam um modelo de transtorno do pânico que se baseia nos efeitos da hiperventilação aguda e crônica, característicos do subtipo respiratório de transtorno do pânico. O modelo é generalizado a partir desses efeitos. Ele integra três características da hiperventilação: a hiperventilação é uma resposta fisiológica à hipercapnia; a hiperventilação pode induzir ataques de pânico; a hiperventilação crônica representa um mecanismo protetor contra os ataques de pânico.* *Método*: *Revisão seletiva da literatura a partir da base de dados Medline. Foram selecionados relatos referentes à inter-relação entre transtorno do pânico, hiperventilação, acidose, alcalose, liberação de catecolaminas e sensibilidade a catecolaminas, sendo os achados estruturados de modo a formar um modelo integrado.* *Discussão*: *Os ataques de pânico do transtorno do pânico desenvolvem-se com base numa acidose metabólica, que é uma resposta compensatória à hiperventilação crônica. Os ataques são desencadeados por um súbito aumento da pressão parcial de dióxido de carbono (pCO_2), quando a acidose (metabólica) latente se manifesta pela acidose hipercápnica. A condição acidótica induz liberação de catecolaminas. A simpaticotonia não pode manifestar-se durante a fase de hipercapnia, pois o baixo pH diminui a sensibilidade às catecolaminas. As catecolaminas podem provocar pânico quando a hipercapnia comuta para uma alcalose hipocápnica devido à supercompensação pela hiperventilação, situação na qual a sensibilidade às catecolaminas liberadas começa a aumentar.* *Conclusão*: *As abordagens terapêuticas deveriam voltar-se para a regulação em longo prazo do padrão respiratório e a eliminação da acidose metabólica.*

Descritores: *Acidose; Catecolaminas; Hiperventilação; Hipocapnia; Transtorno de pânico*

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Introduction

Although the correlation between the respiratory panic disorder (PD) subtype and hyperventilation is well established in the literature, the active role of hyperventilation in the pathomechanism of PD is less understood. Although Wilhelm et al. provided a thorough review of the three main theories on the role of hyperventilation in PD,[1] they identified contradictions among them and did not offer a synthesis of the current concepts. The increase of tissue H^+ ion concentration, which is regulated promptly and effectively by respiration-induced changes in pCO_2, is a strong stimulus of catecholamine release. However, acidotic conditions decrease the catecholamine sensitivity of target organs (the inverse of what occurs in alkalosis). In a panic attack, these events occur in rapid succession. Therefore, understanding the timing and the time constant (how quickly a change develops) of physiological variables is crucial for resolving the apparent contradictions and establishing a coherent model.

The role of hypocapnia in the pathomechanism of PD has been largely overlooked in the literature.[2] During the late 1930s, hyperventilation played a central role in the diagnostic formulation of hyperventilation syndrome.[3-4] Shortly after the conceptualization of PD in the DSM III (1980), it became evident that there had been an overlap between symptoms of hyperventilation syndrome and PD.[5] The article written by Klein in 1993 represented an important step toward settling the long-standing debate on the role of hyperventilation.[6] Klein denied the importance of acute or chronic hyperventilation in the generation of panic attacks. Although he described a positive correlation between chronic hyperventilation and panic attacks, he used this observation in order to put forth the idea that chronic hyperventilation is protective against panic.

The aim of this study was to review the literature on PD, with a special focus on the role of hyperventilation and hypocapnia in the pathomechanism of PD. Special attention was paid to studies investigating the interrelationships between panic, pH, pCO_2, tissue catecholamine sensitivity, and catecholamine elimination, as well as their temporal characteristics.

Method

We conducted a selective review of the literature in the Medline database, limiting our searches to articles published between 1937 and 2006. Our approach was to discuss the available literature on PD in order to show that it is not only a psychiatric disorder but also a regulatory disorder. Our first search included the terms "panic" and "hyperventilation", and/or "hypocapnia" and/or "hypercapnia". This search strategy yielded a total of 317 articles, from which we selected 33 for analysis. In selecting these articles, our principal aim was to represent all major opinions and trends. Within this context, we selected articles written by the most prominent authors. Therefore, these articles and their main arguments present a logical progression. In addition, we reviewed the most controversial papers. Furthermore, 17 of the articles included deal with the physiology and pathology of catecholamine homeostasis in relation to panic. These articles were identified by adding the search terms "acid-base disorder", "acidosis", "alkalosis", "hypocapnia", "hypercapnia", "catecholamine", "noradrenaline", "adrenaline", and "sympathetic nervous system". In this step of the selection process, we focused on articles investigating the relationship between acidosis/alkalosis and catecholamine production, as well as on those investigating the catecholamine sensitivity of brain and other tissues in relation to pH. We also included 10 articles on psychiatric topics presenting borderline relationships with PD. The search of the literature and the article selection were carried out by András Sikter, who has been researching this topic for decades and therefore has profound insight into the issue. The author notes on the articles evaluated have been arranged into a logical order so that they can be integrated into a coherent model.

Discussion

Maintaining the homeostasis of intracellular and extracellular pH is a crucial regulatory task for the organism. A couple of deep breaths can substantially decrease CO_2 concentration, increasing extracellular pH to 7.4-7.7. Since CO_2 readily passes through cell membranes, intracellular pCO_2 decreases to the same degree. Therefore, altering respiration can produce marked changes in intracellular pH, the consequences of which are outlined below.[7] Acute hypocapnia has a progressive effect on membrane permeability, metabolism, oxygen consumption, and cardiac function,[8] as well as exciting the nervous system through the hypopolarization of neurons.[9-10] In contrast, hypercapnia results in decreased cell membrane permeability,[11] metabolic depression,[12] reduced muscle contractility[13], and hyperpolarization of neurons. In short, acute hypocapnia elicits effects similar to those seen when the sympathetic nervous system is stimulated, whereas acute hypercapnia evokes parasympathetic effects. The latter occurs despite the fact that hypercapnia causes increases in the levels of serum adrenaline and noradrenaline.[14] There are conflicting data in the literature regarding serum adrenaline and noradrenaline levels in acute hypocapnia, some authors reporting no alterations[14] and others demonstrating significant decreases.[15] Hypoxia is a disturbing variable in most investigations.[16] Catecholamine sensitivity decreases in hypercapnic acidosis and increases in hypocapnic alkalosis.[7] These changes in catecholamine level and sensitivity affect target organs. Lower intracellular pH is the trigger for noradrenaline release from the locus coeruleus during panic attacks.[17-18]

Chronic hypocapnia elicits a cascade of changes due to compensatory mechanisms for the restoration of intracellular and extracellular physiological pH. Renal reabsorption of chlorine ions and excretion of bicarbonate is increased in sustained hypocapnia.[19] In an experimental model of hyperventilation in dogs, it was shown to take five days for the kidneys to reestablish the equilibrium.[20] In humans, the role of intracellular buffer mechanisms is more important, and adaptation to chronic hyperventilation or hypoventilation is therefore less dependent on renal function.[21] The process of adaptation is similarly slow: to regain equilibrium can take five to seven days.[7] It takes equally as long to reverse the changes after the occurrence of eucapnia. Buffer mechanisms include the release of hydrogen ions, which shifts pH toward the physiological level, although this process also occurs only after a delay.

Various authors have downplayed the role of hyperventilation in PD and have recommended that the term 'hyperventilation syndrome' no longer be used.[21-24] However, in another review article, Gardner argues for the preservation of the term.[25] Other authors have stated that chronic hyperventilation is a common cause of both hyperventilation syndrome and PD.[5,25-26] Recently, Nardi addressed the role of hyperventilation in PD and tried to

clarify it, stating that it is considered to be "...a cause, a correlate, or a consequence of panic attacks." According to Nardi, acute hyperventilation might play a role in the pathomechanism of the respiratory PD subtype.[27]

In a study using transcutaneous monitoring, no relationship was found between PD and hyperventilation.[28] This method is outdated due to its high inertia (slow decay) in monitoring changes in arterial pCO_2.[2] It is widely accepted that the respiratory PD subtype, which accounts for approximately 50% of all PD cases, is closely related to hyperventilation and represents a hyperventilation syndrome comorbidity.[2,5,25-26]

There are three views in the literature regarding the role that hyperventilation plays in the pathomechanism of PD. In the first, panic is triggered by elevated CO_2 levels, and hyperventilation follows as a physiological response.[1,29] In this model, the hyperventilation is a consequence, an epiphenomenon observed during naturally-occurring and drug-induced panic attacks. In the view of other authors[30-31] – a view shared by followers of the cognitive-behavioral theory of PD[1] – hyperventilation-induced hypocapnia plays a central role. The opinion of psychotherapists can be summarized as follows: individuals with PD can misinterpret the bodily sensations caused by hyperventilation as being indicative of life-threatening danger.[32]

However, the most widely accepted view is that detailed by Klein[6]: hyperventilation is a protective mechanism against panic reactions. In his thorough study, Klein demonstrated that patients with PD are hypersensitive to increases in pCO_2, and that panic attacks are triggered by a relative increase in the level of CO_2. Such individuals present chronic hyperventilation as a means of avoiding the panic-inducing increase in CO_2 levels.

We agree with Klein that chronic hyperventilation has some defensive effects against panic attacks in individuals with PD, since a sudden increase of pCO_2 (e.g. CO_2 challenge) has been shown to provoke such attacks.[33] However, chronic hyperventilation is always accompanied by compensatory metabolic acidosis. In an individual with chronic hyperventilation, life events (i.e., relaxation, sleep, premenstrual phase, etc.) can cause pCO_2 to rise to the normal baseline or above.[6] The latent metabolic acidosis then appears, and the elevated concentration of H^+ increases CO_2 sensitivity of the respiratory center. It can be assumed that the chronic hyperventilation itself is responsible for the increased CO_2 sensitivity observed in individuals with PD.

The best supporting evidence is provided by Klein himself, who found chronic hyperventilation to correlate positively with lactate-induced panic and CO_2 sensitivity.[6] Hypophosphatemia, which is an indicator of chronic hyperventilation, has been found to be predictive of lactate-induced panic attacks.[34] Decreased plasma bicarbonate is also a marker of chronic hyperventilation and sensitizes to the onset of panic attacks.[35] However, chronic hypercapnia accompanied by metabolic alkalosis has been shown to correlate negatively with the development of panic attacks.[6]

Various researchers have been successful in using hyperventilation to provoke panic attacks.[27,36-39] Nardi addressed the role of hypocapnia and hypercapnia in PD with equal focus and equal importance in the pathogenesis.[27,38-39] However, the overall effect of hyperventilation on panic was significantly less than that of CO_2 inhalation. Respiratory challenge tests (CO_2 and breath-holding) can provoke panic attacks in individuals presenting the respiratory PD subtype.[39] Cerebral hypoxia, chronic hyperventilation, and anxiety persist in the interim between panic attacks.[26] Although individuals with PD are prone to continue hyperventilating,[1,32] the hyperventilation facilitates panic attacks.

Caldirola stated that an irregular breathing pattern is predictive of PD, and that similar irregularity can be found in generalized anxiety disorder.[40] The similarity can explain the high comorbidity of these two conditions.[26] In individuals with generalized anxiety disorder, the irregularity of breathing is less pronounced than in those with PD.[41] Various studies have shown that, in individuals with PD, there is a strong correlation between the degree of respiratory irregularity and the frequency of panic attacks, as well as between such irregularity and CO_2 vulnerability.[1,41-42] Irregular respiration occasionally causes elevated pCO_2, which can trigger a panic attack.

The hypothalamic-pituitary-adrenocortical axis model of hypercapnia induced panic is generally accepted in the literature,[17,43] although it was recently questioned by Gorman,[44] who discovered inconsistencies and pointed out that, during CO_2 challenge, actual pCO_2 values correlate negatively with signs and symptoms of panic. This indicates that panic develops not during hypercapnia but during the subsequent hypocapnic phase. The way Gorman puts it: "...in panic disorder patients, we have found that elevated cortisol, fear and hypocapnia are intercorrelated in the few minutes before actually experiencing an acute attack."

As previously mentioned, higher pCO_2 leads to increased noradrenaline release.[18] However, in human plasma, noradrenaline has a half-life of only a few minutes.[45-46] In the rebound phase of hypocapnia, cells present increased sensitivity to residual catecholamines.[7] Strong catecholamine stimuli are known to induce panic attacks.[47] Individuals with PD present normal catecholamine levels between panic attacks.[48] It is therefore possible that, in addition to the hypercapnia-related increase in catecholamine levels, the hypocapnia-induced catecholamine sensitivity plays a significant role in the induction of panic.[49]

Borelli et al. conducted electrophysiological studies in animals[50] and concluded that panic attacks represent a pathological manifestation of 'freezing behavior' (low-arousal condition), rather than the high-arousal condition of the 'fight-or-flight' response.[51] 'Freezing behavior' initially manifests as immobility, bradycardia, and hypoventilation but can transform into the flight response, which is characterized by vigorous locomotion, tachycardia, and hyperventilation.[52] The sudden change in the respiratory pattern that precedes the flight response indicates the similarity with panic attacks. It is quite probable that the role the brainstem plays in the pathomechanism of PD is more important than previously suggested.

We can build a profile of PD that integrates the three hyperventilation theories. Individuals with the respiratory PD subtype present chronic hyperventilation. The chronic hyperventilation results in a compensatory decrease in intracellular and extracellular pH due to renal secretion of bicarbonate and due to the tissue buffer mechanisms. A balanced steady-state is established between the hypocapnic alkalosis and the metabolic acidosis. Multiple factors can lead to a sudden increase in CO_2 levels. In individuals with PD and presenting sustained hypoventilation episodes, irregular breathing causes abrupt changes in pCO_2. In the prelude to a panic attack, an abrupt increase of pCO_2 occurs, which leads to unusually high intracellular H^+ concentrations, thereby triggering the release of noradrenaline in the locus coeruleus. This sudden increase in intracellular acidosis elicits hypocapnia by compensatory

hyperventilation. In addition, individuals with PD overcompensate for hypercapnia.[53] The consequence is severe sympathicotonia, since the higher catecholamine level resulting from the previous hypercapnia overlaps with the increased catecholamine sensitivity caused by the hypocapnic alkalosis. The adrenergic/noradrenergic tonus results in fear mediated by the limbic system, and the expectation of threat can create a vicious circle. Long after the chemical component phase of a panic attack is over, the cortical excitation persists, leaving the individual with a lingering, subjective feeling of anxiety. Hyperventilation pushes the individual toward progression of the panic attack.

The profile is supported by various observations. Gorman noted that, in the case of CO_2 challenge, signs and symptoms of panic correlated inversely with pCO_2.[44] One dose of biperiden (an antimuscarinic agent) can prevent panic attacks induced by CO_2 inhalation, since it eliminates the rebound hyperventilation response mediated via the muscarinic receptors of the ventral medulla.[54] Therapies proven to be effective in PD, such as cognitive therapy, biofeedback, and antidepressant pharmacotherapy, seem to also be useful in hyperventilation syndrome.[55-57] Successful pharmacotherapy of panic attacks normalizes blood gas parameters, i.e. it eliminates hyperventilation as well as the increased CO_2 sensitivity characteristic to PD.[58]

Conclusion

Taken separately, each of the three hyperventilation theories can correctly interpret one step in the pathological dynamics of panic attacks. Chronic hyperventilation predisposes an individual to PD, since compensatory mechanisms (such as alterations in renal function and tissue buffer capacity) lead to chronic metabolic acidosis, which remains latent until it is activated by chronic hypocapnia. The acidosis manifests when hyperventilation decreases or hypercapnia develops[6] (metabolic + respiratory acidosis). Acidosis induces catecholamine release, and the activity of locus coeruleus increases. Therefore, panic attacks can be triggered by the mitigation or elimination of chronic hyperventilation, with a consequent elevation of pCO_2. Due to the decreased tissue catecholamine sensitivity developed during acidosis, the catecholamine release does not cause an abrupt increase in sympathetic activity during this phase. Hypercapnia is compensated for – frequently overcompensated for – by acute hyperventilation.[29] Sympathicotonia develops when the acute hypocapnia makes the tissues sensitive to the circulating catecholamines, the elimination of which has a time lag measured in minutes. Patients with PD react with panic to extreme sympathicotonia, a reaction that involves cognitive mechanisms.[59] When chronic hyperventilation is followed by acute hypoventilation (hypercapnia) and this hypoventilation is followed by (over)compensatory hyperventilation (hypocapnia), acute hyperventilation can provoke panic.

The pathogenesis of panic attacks can include defensive mechanisms resembling 'freezing behavior', since prolonged hypercapnia induces strong catecholamine release. However, but the sympathetic response arises when tissue catecholamine sensitivity increases due to subsequent hyperventilation.[50]

The respiratory PD subtype can be explained by the different time constants of chemical processes: pCO_2 and pH changes are immediate, the elimination of catecholamines from blood takes only minutes, and the clearance of metabolic acids can require several days. Chronic hyperventilation, together with the corresponding metabolic acidosis, is a predisposing factor for PD. Therefore, therapeutic approaches should address long-term regulation of respiratory patterns[60] and elimination of metabolic acidosis.

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