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ORIGINAL ARTICLE

The panic disorder respiratory ratio: a dimensional approach to the respiratory subtype

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Abstract
Objective: The respiratory ratio is a dimensional construct of the respiratory subtype of panic disorder (PD). The respiratory subtype has been correlated with an increased sensitivity to CO_2 inhalation, positive family history of PD and low comorbidity with depression. The objective of our study was to determine whether the respiratory ratio is correlated with CO_2-induced panic attacks and other clinical and demographic features. *Methods:* We examined 91 patients with PD and submitted them to a double-breath 35% CO_2 challenge test. The respiratory ratio was calculated based on the Diagnostic Symptom Questionnaire (DSQ) scores recorded in a diary in the days preceding the CO_2 challenge. The scores of the respiratory symptoms were summed and divided by the total DSQ score. *Results:* The respiratory ratio was correlated with CO_2 sensitivity, and there was a non-statistically significant trend towards a correlation with a family history of PD. *Conclusions:* The positive correlation between the respiratory ratio and the anxiety elicited by the CO_2 inhalation indicates that the intensity of respiratory symptoms may be proportional to the sensitivity to carbon dioxide.

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Introduction

According to the DSM-IV,[1] panic disorder (PD) is a unitary diagnostic category. Nevertheless, within this category, there are diverse clinical presentations, leading to concerns that PD is not a singular diagnosis.[2] As a response to these concerns, alternative classification schemes have been devised.[2] Authors have proposed that the subtypes should be defined by the most prominent symptoms during a typical panic attack (PA), such as respiratory, cardiovascular, and gastrointestinal subtypes.[3] Respiratory abnormalities, such as increased sensitivity to CO_2, are associated with PD, and there may be a connection between the respiratory subtype of PD and these abnormalities.[4,5]

Klein[6] proposed that spontaneous PAs occur when the brain's suffocation monitor erroneously signals a lack of useful air, maladaptively triggering an evolved suffocation alarm system. Such a dysfunction would make an individual vulnerable to "false suffocation alarms", namely, PAs. Respiratory tests have been fruitful in generating hypotheses about PD,[6,7] indicating that CO_2 sensitivity may be part of a hypersensitive suffocation detector.[6] PD patients exhibit both behaviorally and physiologically abnormal responses to respiratory challenge tests.[8,9] The CO_2 inhalation increases pCO_2 and reduces pH in the blood, changes that are also observed in the brain.[10] Some regions of the brain that are sensitive to $H+/CO_2$ have been implicated in both ventilation control and defensive behaviors, including panic. The increase of CO_2 and H+ in the brain may activate these structures, inducing PAs and increasing ventilation.[10]

The administration of 1 or 2 vital capacity breaths of a 35% CO_2/65% O_2 mixture to patients with PD is a brief but intense stimulation, accompanied by neurovegetative symptoms similar to real-life PA symptomatology.[11,12] These respiratory tests induce dose-dependent anxiety and panic symptoms in many subjects with and without PD,[10,13,14] but in PD patients, this response is significantly more intense.[11,12,15] In addition, healthy first-degree relatives of PD patients react significantly more to CO_2 inhalations than do healthy subjects without a family history of PD.[16] The research on CO_2 challenge tests strongly suggests a relationship between the pathophysiology of PD and some disturbance in breathing control.[4,11] Recent studies indicate that patients with the respiratory subtype of PD are more sensitive to 35% CO_2 challenge tests and hyperventilation tests than subjects without this subtype.[17-19] Hypersensitivity to CO_2 and prominent respiratory symptoms might be markers for genetic vulnerability to respiratory PD.[5,16]

Briggs et al.[20] defined the respiratory subtype of PD as a distinct subgroup of PD patients with prominent respiratory symptoms. Respiratory subtype patients are more likely to have a family history of PD and exhibit low comorbidity with depression, longer illness duration and low neuroticism scores.[5] These patients also exhibit higher scores on PD severity scales, and the improvement with pharmacological treatment is observed more quickly than in patients without this subtype.[20,21] Controversial findings also exist regarding the respiratory subtype, such as the correlation with the age of onset, tobacco and alcohol use.[5]

A principal component analysis with PD symptoms conducted by Briggs et al.[20] determined that the presence of the fear of dying, chest pain/discomfort, shortness of breath, paresthesias, and feelings of choking during a PA defined a distinct subgroup of PD patients. If at least four of the five respiratory symptoms were present in a given patient, he or she was considered to have the respiratory subtype.[20] Throughout the years, many studies[17-19,21-23] have been based on Briggs's classification, but none of the studies addressed two important problems: the classification does not account for the intensity of the respiratory and non-respiratory symptoms; and patients with many symptoms have an increased chance to be classified with the respiratory subtype. With Briggs' classification, patients with marked gastrointestinal or neurologic symptoms may report mild respiratory symptoms and be incorrectly classified in the respiratory subtype. On the other hand, if a patient has strong feelings of choking, shortness of breath and chest discomfort but does not experience paresthesias and fear of dying, he will not be diagnosed with the respiratory subtype. A method that accounted for the intensity of symptoms would lead to a more reliable classification of patient samples. Consistent findings are reported in patients with the respiratory subtype, such as a positive family history and high sensitivity to CO_2 challenge tests.[18,19,23] However, PD studies report conflicting findings regarding the age of onset and comorbidities.[24] These inconsistencies may be due to the limitations of the Briggs' classification.

The prevailing systems of classification of psychiatric disorders assume that the categorical representation is appropriate; disorders are laid out as distinct types and diagnosed as present or absent. However, some authors propose that dimensional taxonomy should be used in at least some conditions.[25] Studies indicate that dimensional constructs may be superior to categorical classifications because in addition to capturing the core symptoms, dimensional constructs capture the subtle psychopathology of anxiety disorders.[25,26] Dimensional variation exists between and within categories, and quantitative variation can be simplified into categorical distinctions,[25] such as the respiratory subtype.

In the current study, we defined the respiratory ratio, a dimensional correlate of the respiratory subtype, as the ratio between the respiratory and the non-respiratory symptoms occurring during PA, accounting for the intensity of each symptom. We hypothesize that the respiratory ratio is correlated with high sensitivity to CO_2 challenges, positive family history of PD and a low prevalence of major depression. The objective of this study was to ascertain whether the respiratory ratio can predict CO_2-induced PAs and whether the respiratory ratio is correlated with specific clinical and demographic features in PD patients. This study is the first attempt to build a body of evidence concerning the respiratory ratio.

Methods

Subjects

In the current study, a database from a previous research project[27] was used. Patients with a diagnosis of PD with agoraphobia were consecutively recruited as they presented to the Laboratory of Panic and Respiration at the Institute of Psychiatry of the Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. The data collection for the original study lasted for approximately six months. After subjects

received a clinical diagnosis of PD, made by an expert psychiatrist, they were interviewed by a second psychiatrist with the Structured Clinical Interview Diagnostic[28] for DSM-IV.[1] If the two clinicians disagreed on the diagnosis, they met to confer. If a consensus on the diagnosis could not be reached, the subject was not enrolled. Patients who met the DSM-IV criteria for current major depression, bipolar disorder, obsessive-compulsive disorder, schizophrenia, delusional or psychotic disorders, organic brain syndrome, severe personality disorder, suicide risk, epilepsy, or substance abuse or dependence (during the previous year) were excluded. Patients with comorbid dysthymia, generalized anxiety disorder, or past major depression were included if PD was judged to be the principal diagnosis. The protocol was explained to the subjects, who signed a voluntary written consent form to participate in the study. The subjects were informed that the procedure was not dangerous, but that anxiety symptoms could occur during the test. Our local ethics committee approved the protocol (approval number CAAE-0008.0.249.000-05, 14/2005), which complied with the principles of the Declaration of Helsinki. The inclusion criteria selected 18 to 55 years of age; both genders; occurrence of at least three PAs in the two weeks before the challenge test day and no use of any psychotropic drugs for at least one week by any subject. Exclusion criteria included unstable medical condition; cognitive-behavior psychotherapy during the study; use of any regular antipsychotic, antidepressant, regular benzodiazepine or non-benzodiazepine anxiolytic medication for four weeks before the use, the use of fluoxetine for five weeks before the test or a positive urine test for benzodiazepines or other drugs before the test. Subjects with a history of respiratory disease and smokers were also excluded. All subjects underwent a physical examination and laboratory examinations to ensure that they were healthy enough to participate in a CO_2 challenge test. The patients had no respiratory or cardiovascular abnormalities and were free of caffeine ingestion for one day. All subjects filled out a form with sociodemographic and clinical data, including age, gender, education, occupation, marital status, family history of PD and age of onset of PD. The family members were not examined.

Measures

The Subjective Units of Disturbance Scale (SUDS) is a quantitative evaluation method ranging from 0 (no anxiety) to 10 (maximum anxiety).[29] The Diagnostic Symptom Questionnaire (DSQ) is a list of 13 PA symptoms adapted from DSM-IV1 in which the presence and level of discomfort of each panic symptom experienced after the inhalations is rated on a 0- (none) to 4-point (very severe) scale, and the total score ranges from 0 to 52.[30] Both the SUDS and DSQ were used in the CO_2 inhalation procedure. To avoid baseline interference in the quantitative assessment of the SUDS measurements, the percentage of maximum increase or decrease possible in the SUDS score (PMIDPSUDS) was calculated.[31] The ΔSUDS was calculated as the difference between the SUDS score after the CO_2 inhalation (SUDS2) and the SUDS score before the inhalation (SUDS1). If the ΔSUDS was negative, the PMIDPSUDS was equal to the ΔSUDS divided by SUDS1. If the ΔSUDS was positive, the PMIDPSUDS was equal to the ΔSUDS divided by the difference between the maximum SUDS score (10) and SUDS1.[31]

During this first visit to our research center, each patient received a diary in which they recorded any PAs that occurred between the screen visit and the visit for the CO_2 test one week after. The respiratory ratio was calculated based on the DSQ scores of non-induced PAs registered in the diary. The scores of the respiratory symptoms (fear of dying, chest pain/discomfort, shortness of breath, paresthesias, and feelings of choking) were summed and divided by the total DSQ score for each patient.

Procedure

Before the inhalations, all subjects were asked to relax for 10 minutes. Respiratory frequency, pulse, and blood pressure were checked, and the measurements were repeated 1 and 5 minutes after the test. Using a double-blind (patient and medical raters) design setup, the patients inhaled the 35% CO_2 mixture or atmospheric compressed air, randomly selected with a coin flip by an independent staff member. The same test procedure was repeated after 20 minutes using other gas (i.e., 35% CO_2 or compressed air). During the test procedure, the patients exhaled as fully as possible, placed the inhalation mask, took a fast vital capacity breath, held their breath for 8 seconds, exhaled, and repeated the fast vital capacity breath, again holding for 8 seconds. The compliance with the tests was established by the three members of our team who attended present during the tests. Both tests were attended by one medical staff member who dealt with the patient and the gases (independent staff member) and by two test-blind rater psychiatrists. To measure the anxiety level before and after the CO_2 inhalation, we asked the subjects to complete the SUDS. The DSQ was also completed after the respiratory challenge.

Based on the DSQ, a CO_2-induced PA was defined as the following: (1) the presence of 4 or more DSM-IV PA symptoms, where either the presence or the increase in DSM-IV symptomatology was used for diagnosis; (2) at least one DSM-IV cognitive panic symptom, that is, fear of dying, losing control, or going crazy; (3) the patient's statement that the sensation of panic or fear after the test resembled a spontaneous PA; and (4) an agreement of 2 medical doctors blind to whether the patient was receiving CO_2 or compressed air that the patient had a clinical PA. The SUDS scores were not used for diagnosing a PA. All of these criteria were used in the diagnosis of a PA to increase the reliability and clinical significance.

Statistical analysis

To calculate the correlations between the respiratory ratio and the other variables, the authors used the Pearson Correlation Coefficient for continuous variables with normal distributions, the Spearman's Rank Correlation Coefficient for ordinal variables and continuous variables without normal distributions and the Point-Biserial Correlation (PBC) to correlate continuous and dichotomous variables. The PBC is a special case of the Pearson Correlation Coefficient in which a continuous variable is correlated with a true dichotomy. The correlation coefficients were considered small when approximately .10, medium when .30 and large when .50.[32]

Responders and non-responders to the CO_2 challenge were compared with respect to their respiratory ratio and demographic and clinical features. The Student's t-test was used to compare the means of numeric variables between the two groups, and the chi-square test was used to compare categorical variables.

To ascertain the predictive value of the respiratory ratio, the ROC curve was analyzed. A respiratory ratio cutoff was defined based on the smallest difference between the sensitivity and specificity values. The positive predictive value and negative predictive value were calculated.

All analyses were two-tailed, and the level of statistical significance was set at 5%.

Results

A sample of 91 patients with PD was included in the trial. A total of 62 patients with PD (68.1%) suffered a PA after the CO_2 test (responders), and 29 patients with PD (31.9%) did not suffer a PA after the test (non-responders).

In our sample, we did not reject the normality hypothesis of the respiratory ratio (Kolmogorov Smirnov Z, p = .872), and the mean was .458 (SD = .104), indicating that the respiratory symptoms represented approximately 45.8% of the PD symptoms registered in the diary of all patients. The respiratory ratio exhibited moderate positive correlations with PMIDPSUDS and the response to CO_2 inhalation. We also observed trends towards positive correlations with SUDS2 and family history and a negative correlation with education (Table 1).

The hypothesis of normality was rejected for PMIDPSUDS (Kolmogorov Smirnov Z, p = .003) and SUDS2 (Kolmogorov Smirnov Z, p < .001), and linear regression based on normality was not possible using these variables. Although it would have been possible to use a nonparametric regression, it would have been difficult for psychiatrists to read. We decided not to base our conclusions on linear regressions.

Table 1 Correlations of the respiratory ratio.

Variable	Method	Correlation strength
Gender	PBC	.017
Age	Pearson	.169
Education	PBC	-.183 *
Occupation	PBC	.138
Marital status	PBC	.142
Family history	PBC	.189 *
Age of onset	Pearson	-.089
MDD	PBC	.086
DSQ	Pearson	.107
SUDS1	Spearman	-.095
SUDS2	Spearman	.198 *
PMIDPSUDS	Spearman	.236
CO_2PA	PBC	.334 **

PBC: Point-biserial correlation; Pearson: Pearson correlation coefficient; Spearman: Spearman's rank correlation coefficient; MDD: Previous major depressive disorder episodes; SUDS1: SUDS score before the CO_2 inhalation; SUDS2: SUDS score after the CO_2 inhalation; PMIDPSUDS: Percentage of maximum increase or decrease possible in the SUDS scale; corresponds to the anxiety increase induced by the CO_2 inhalation; CO_2PA: CO_2-induced panic attack.
* p < .1; ** p <.01.

The patients who suffered PAs after the CO_2 inhalation exhibited significantly higher respiratory ratios. The responders were significantly more likely to exhibit a family history of PD, a lower age of onset and a higher prevalence of previous major depression episodes. As expected, the SUDS2, PMIDPSUDS and DSQ were significantly higher for the responders compared to the non-responders. There were no differences in sex, age, education, marital status, or occupation between the groups (Table 2).

To determine how well the respiratory ratio could predict CO_2-induced Pas, the ROC curve was calculated. The area under the curve (AUC) was .707, and the respiratory ratio cutoff was .437. Using this cutoff, the sensitivity was 67.7%, the specificity was 65.5%, the positive predictive value was 80.8% and the negative predictive value was 48.7%.

Discussion

The respiratory ratio was correlated with CO_2 sensitivity. A non-statistically significant trend towards a correlation between the respiratory ratio and a family history of PD was observed. A positive family history of PD, comorbidity with major depression and an early age of onset were correlated with the response to carbon dioxide inhalation.

In the current study, prominent respiratory symptoms were correlated with a high sensitivity to CO_2, consistent with the findings of previous studies.[17,18,27] Biber and Alkin[17] observed that 35% CO_2 inhalation induced PAs in 79% of patients with the respiratory subtype, whereas only 48% of patients with the non-respiratory subtype suffered PAs during the respiratory challenge. Valenca et al.[18] observed that 93.7% of patients with the respiratory subtype suffered PAs during 35% CO_2 inhalation, whereas only 43.4% of patients with the non-respiratory subtype suffered PAs, indicating a higher sensitivity to CO_2 in patients with the respiratory subtype. In a study using a 5% CO_2 rebreathing challenge,[22] more respiratory subtype patients than non-respiratory subtype patients terminated the procedure voluntarily. Respiratory subtype patients also exhibited a higher respiratory frequency and more suffocation sensations than non-respiratory subtype patients.[22] The intensity of respiratory symptoms in PD patients may be proportional to the sensitivity to CO_2, and a slight increase in CO_2 levels might be misinterpreted as a lack of useful air, triggering PD symptoms.

Another interesting finding from the current study is that the responders exhibited a higher family prevalence of PD than did the non-responders. Perna et al.[16] described the treatment-seeking PD probands, their first-degree relatives, and the relatives of normal controls. Although relatives with a personal history of any mental disorder were excluded, 22% of those related to PD probands developed a PA after one inhalation of 35% CO_2. Fifty-one percent of the PD probands but only 2% of the relatives of normal controls developed PAs as well. Thus, high-risk relatives were significantly less likely to develop PAs with CO_2 than were ill probands.[16] In a similar study, 44% of the first-degree relatives of PD patients exhibited PAs after one inhalation of 35% CO_2, whereas only 12% of the controls exhibited PAs.[33] Bellodi et al.[34] conducted a twin study that generated strong evidence for the role of genetic factors in the sensitivity to CO_2 inhalation. If it could

Table 2 Clinical features of responders and non-responders to the CO_2 inhalation.

		No CO_2-induced panic attack		CO_2-induced panic attack	
		n / Mean	% / SD	n / Mean	% / SD
Total		29	31.9	62	68.1
Gender	Male	12	41.4	24	38.7
	Female	17	58.6	38	61.3
Age		36.8	9.3	39.4	10.0
Education	Low	9	31.0	16	25.8
	High	9	69.0	46	74.2
Ocupation	Inactive	14	48.3	26	41.9
	Active	15	51.7	36	58.1
Married		17	58.6	41	66.1
Family history *		11	37.9	40	64.5
Age of onset **		30.4	6.1	23.2	5.1
MDD **		13	44.8	47	75.8
Respiratory ratio **		.407	.094	.481	.100
DSQ **		12.8	2.2	17.7	2.8
SUDS1		3.4	2.6	2.9	1.8
SUDS2 **		3.4	1.6	8.4	1.4
PMIDPSUDS (%) **		-6.8	33.0	77.0	19.8

MDD: Previous major depressive disorder episodes; DSQ: Diagnostic Symptom Questionnaire score; SUDS1: SUDS score before the CO_2 inhalation; SUDS2: SUDS score after the CO_2 inhalation; PMIDPSUDS: Percentage of maximum increase or decrease possible on the SUDS scale; corresponds to the anxiety increase induced by the CO_2 inhalation.
* p< .05; ** p< .005.

be established that an abnormal sensitivity to CO_2 comprises a marker for PD, the test could be used to identify individuals with a relatively high risk for the onset of spontaneous PAs.

Although the current study failed to demonstrate a strong association between the respiratory ratio and a family history of PD, there is evidence in the literature of an association between genetics and respiratory symptoms. Studies indicate that 62.1% to 71.4% of PD patients with the respiratory subtype have a family history of PD, whereas only 31.3% to 37.9% of patients without the respiratory subtype have a first-degree relative with this disorder.[19,23,27] Studies of the genetics of PD suggest that the respiratory subtype may be an important biological marker, although none of these studies have addressed this question directly.[5] In the current study, the correlation between the respiratory ratio and a family history of PD did not reach statistical significance, but future studies, with larger samples, may identify this association.

The main limitations of this study were the small sample size and the lack of equipment to confirm that the subjects inhaled full vital capacities of 35% CO_2 and air during the experiment.

Conclusion

The positive correlation between the respiratory ratio and the PD symptoms elicited by the CO_2 inhalation indicate that the intensity of respiratory symptoms may be commensurable with the sensitivity to carbon dioxide. The respiratory ratio may be a useful tool in the research of PD as a bridge connecting the psychopathology to the underlying neurobiology.

Disclosures

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References

1. APA. Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV). 4 ed. Washington, DC: American Psychiatric Press; 1994.
2. Beck JG, Shipherd JC, Ohtake P. Do panic symptom profiles influence response to a hypoxic challenge in patients with panic disorder? A preliminary report. Psychosom Med. 2000;62(5):678-83.
3. Aronson TA, Logue CM. Phenomenology of panic attacks: a descriptive study of panic disorder patients' self-reports. J Clin Psychiatry. 1988;49(1):8-13.
4. Nardi AE, Freire RC, Zin WA. Panic disorder and control of breathing. Respir Physiol Neurobiol. 2009;167(1):133-43.
5. 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.
6. Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. Arch Gen Psychiatry. 1993;50(4):306-17.
7. Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. Am J Psychiatry. 2000;157(4):493-505.
8. Papp LA, Klein DF, Gorman JM. Carbon dioxide hypersensitivity, hyperventilation, and panic disorder. Am J Psychiatry. 1993;150(8):1149-57.
9. 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.
10. Esquivel G, Schruers KR, Maddock RJ, Colasanti A, Griez EJ. Acids in the brain: a factor in panic? J Psychopharmacol. 2010;24(5):639-47.
11. Griez EJ, Lousberg H, van den Hout MA, van der Molen GM. CO_2 vulnerability in panic disorder. Psychiatry Res. 1987;20(2):87-95.
12. 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.
13. Colasanti A, Salamon E, Schruers K, van DR, van DM, Griez EJ. Carbon dioxide-induced emotion and respiratory symptoms in healthy volunteers. Neuropsychopharmacol. 2008;33(13):3103-10.
14. Griez EJ, Colasanti A, van DR, Salamon E, Schruers K. Carbon dioxide inhalation induces dose-dependent and age-related negative affectivity. PLoS One. 2007;2(10):e987.
15. 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.
16. Perna G, Cocchi S, Bertani A, Arancio C, Bellodi L. Sensitivity to 35% CO_2 in healthy first-degree relatives of patients with panic disorder. Am J Psychiatry. 1995;152(4):623-5.
17. Biber B, Alkin T. Panic disorder subtypes: differential responses to CO_2 challenge. Am J Psychiatry. 1999;156(5):739-44.
18. Valenca AM, Nardi AE, Nascimento I, Zin WA, Versiani M. Respiratory panic disorder subtype and sensitivity to the carbon dioxide challenge test. Braz J Med Biol Res. 2002;35(7):783-8.
19. 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.
20. Briggs AC, Stretch DD, Brandon S. Subtyping of panic disorder by symptom profile. Br J Psychiatry. 1993;163:201-9.
21. 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.
22. Abrams K, Rassovsky Y, Kushner MG. Evidence for respiratory and nonrespiratory subtypes in panic disorder. Depress Anxiety. 2006;23(8):474-81.
23. 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.
24. Kircanski K, Craske MG, Epstein AM, Wittchen HU. Subtypes of panic attacks: a critical review of the empirical literature. Depress Anxiety. 2009;26(10):878-87.
25. Haslam N. Categorical versus dimensional models of mental disorder: the taxometric evidence. Aust N Z J Psychiatry. 2003;37(6):696-704.
26. Cassano GB, Michelini S, Shear MK, Coli E, Maser JD, Frank E. The panic-agoraphobic spectrum: a descriptive approach to the assessment and treatment of subtle symptoms. Am J Psychiatry. 1997;154(6):27-38.
27. Nardi AE, Valenca AM, Lopes FL, Nascimento I, Veras AB, Freire RC, et al. Psychopathological profile of 35% CO_2 challenge test-induced panic attacks: a comparison with spontaneous panic attacks. Compr Psychiatry. 2006;47(3):209-14.
28. First MB, Spitzer RL, Gibbon M, Williams JBM. Structured Clinical Interview Diagnostic for DSM-IV axis I Disorders - Clinician Version. Washington: American Psychiatric Press; 1997.
29. Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia with corresponding DSM III syndromes. Acta Psychiatr Scand 1986;73:1-37.
30. Sanderson WC, Rapee RM, Barlow DH. The influence of an illusion of control on panic attacks induced via inhalation of 5.5% carbon dioxide–enriched air. Arch Gen Psychiatry. 1989;46:157-62.
31. Perna G, Bertani A, Caldirola D, Di PD, Migliarese G, Bellodi L. Modulation of hyperreactivity to 35% CO_2 after one week of treatment with paroxetine and reboxetine: a double-blind, randomized study. J Clin Psychopharmacol. 2004;24(3):277-82.
32. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-9.
33. van Beek N, Griez E. Reactivity to a 35% CO_2 challenge in healthy first-degree relatives of patients with panic disorder. Biol Psychiatry. 2000;47(9):830-5.
34. Bellodi L, Perna G, Caldirola D, Arancio C, Bertani A, Di BD. CO_2-induced panic attacks: a twin study. Am J Psychiatry. 1998;155(9):1184-8.