

Approximate Entropy of Respiratory Patterns in Panic Disorder

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Objective: Considerable evidence suggests a connection between panic disorder and respiration, but the nature of the respiratory abnormalities in panic disorder remains unclear. The authors investigated the breath-by-breath complexity of respiration dynamics in panic disorder.

Method: Respiratory physiology was assessed in 40 patients with panic disorder and 31 healthy comparison subjects by using a breath-by-breath stationary system for testing cardiorespiratory function. Irregularity in the breathing pattern was determined by applying the approximate entropy index, which is an indicator of the irregularity and the "disorder" of the measure.

Results: The patients with panic disorder showed significantly higher approximate

entropy indexes than the healthy subjects for the measured respiratory parameters. Sighs contributed to the irregularity of breathing patterns but did not account for all the differences in approximate entropy between the patients with panic disorder and the comparison subjects. Anxiety state, severity of illness, and somatic and individual variables such as participation in sports and cigarette smoking did not seem to influence the results.

Conclusions: Patients with panic disorder showed greater entropy in baseline respiratory patterns, indicating higher levels of irregularity and complexity in their respiratory function. Greater respiratory entropy could be a factor in vulnerability to panic attacks.

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Clinical and experimental data suggest a role of the respiratory system in the pathophysiology of panic disorder. This has led to the idea that disorderly respiratory control mechanisms may underlie the occurrence of panic attacks (1, 2). Despite the evidence for a connection between panic attacks and respiration, the nature of respiratory abnormalities remains unclear. Some studies have shown higher respiratory frequency, tidal volume, and minute ventilation and lower baseline end-tidal CO₂ levels in patients with panic disorder than in patients with other anxiety disorders and healthy comparison subjects (3–5), whereas other studies have not confirmed these results (6, 7).

More consistent and specific respiratory abnormalities arose when the breathing patterns of the patients with panic disorder were studied. These patients showed greater irregularity in tidal volume than patients with generalized anxiety disorder (8) and greater irregularity in tidal volume and minute ventilation and a higher rate of breathing pauses than healthy subjects (9–12). The irregularity in breathing pattern has been attributed to frequent sighs (8, 10, 11, 13).

In order to clarify the nature of respiratory abnormalities in panic disorder, we investigated the baseline respiratory functioning of a group of patients with panic disorder and healthy comparison subjects. Since biological systems are characterized by dynamic processes with extensive interactions between multiple inputs, nonlinear

methods are considered the gold standard for measuring the complexity of physiological functions (14). Each physiological signal, such as respiratory or cardiac, usually represents the output of complex mechanisms, including multiple feedback/coupling interactions and inputs from internal and external sources. The moment or linear statistics, such as mean and standard deviation, are unable to analyze the dynamics of complex physiological signals, whereas nonlinear statistics unravel highly significant differences in circumstances in which the former do not distinguish between groups. Many studies (15–18) have demonstrated that nonlinear measures, including fractal dimension, correlation dimension, largest Lyapunov exponent, and approximate entropy, are more valuable than linear measures for studying variability in heart rate. We used the approximate entropy index, a nonlinear measure of irregularity, to study the dynamics of baseline breathing patterns in our subjects. The approximate entropy index has been widely used to study endocrine function (19–21), heart rate (22–24), and respiratory physiology (25). We know of only three studies (26–28) to date that have analyzed data on psychiatric patients by means of the approximate entropy index.

The aim of this study was to unravel possible differences in the breath-by-breath complexity of respiration dynamics between patients with panic disorder and healthy subjects. The contribution of sighing to the irregularity of breathing

patterns was assessed. The effect of variables that might influence breathing patterns was also evaluated.

Method

Subjects

Forty outpatients with panic disorder with or without agoraphobia (21 women and 19 men) and 31 healthy subjects (16 women and 15 men) were recruited from those consecutively referred to the Anxiety Disorders Clinical and Research Unit of San Raffaele Hospital, Milan, over 8 months. The healthy comparison subjects were recruited by advertisements placed around Vita-Salute University.

Psychiatric diagnoses were obtained with the MINI International Neuropsychiatric Interview-Plus for DSM-IV psychiatric disorders (29). The healthy subjects were free of lifetime psychiatric disorders. The presence of concurrent psychiatric disorders, except specific phobias, was an exclusion criterion for the patients with panic disorder. The severity of the patients' clinical symptoms was measured by the Panic-Associated Symptom Scale (30), which assesses panic attacks, anticipatory anxiety, and agoraphobia, and the Fear Questionnaire (31), which assesses agoraphobia, blood-injury phobia, and social phobia.

The exclusion criteria for all subjects were significant concurrent cardiocirculatory or respiratory disease, significant hypertension (systolic blood pressure greater than 180 mm Hg, diastolic pressure greater than 100 mm Hg), and pregnancy or epilepsy, according to a direct physical examination and medical history. The number of subjects regularly practicing sports, the hours of sports activity per week, and the number of smokers were recorded.

Before respiratory assessment, the subjects had to have been without all psychotropic medications for at least 2 weeks. None of the patients had taken fluoxetine in the 6 months before testing. Because many substances can affect respiratory patterns (32), the subjects were asked to refrain from alcohol for at least 36 hours, from beverages or food containing xanthines for at least 8 hours, from nonsteroid anti-inflammatory drugs for at least 36 hours, and from any eating or smoking for at least 2 hours before assessment of respiratory physiology.

All participants gave their written informed consent to the study after a detailed explanation of the entire procedure.

Testing of Respiratory Physiology

Respiration dynamics were assessed by using the Quark b² stationary testing system (Cosmed, Rome), which allows assessment of respiration physiology by monitoring respiratory functioning and pulmonary gas exchange on a breath-by-breath basis. The breath-by-breath recording by the Quark b² system is widely used in sports medicine and respiration physiology studies, in accordance with the recommendations of the American Thoracic Society and the European Respiratory Society (33, 34).

Apparatus. The Quark b² system consists of a mobile unit containing the principal components, which are connected to a computer to allow continuous breath-by-breath recording of respiratory parameters. The principal components are 1) a digital infrared-light turbine that measures respiration air flows, 2) rapid-response O₂ and CO₂ analyzers, 3) electronic sensors measuring barometric pressure, ambient temperature, and humidity, and 4) a humidity absorber. An open, light face mask connects the subject to the respiratory testing system.

Before each test, the turbine and the analyzers were calibrated in order to maintain optimal technical characteristics of the apparatus.

Procedure. The recording of respiratory measures was carried out by physicians (D.C. and G.M.) trained in the use of the Quark b² system. A standardized procedure was used throughout to minimize any confounding influences (32).

The recording was carried out in a quiet room and took 20 minutes. The patients were tested between 4:00 p.m. and 6:00 p.m. to avoid biases related to circadian rhythms of respiratory control (35, 36). Before the recording started, the subjects rested for 20 minutes and were familiarized with the study apparatus.

The subjects were told that the system would assess baseline respiratory physiology and record the respiratory measures during natural breathing at rest. The subjects were instructed to remain seated silently, quietly, and with eyes open during the entire session. They were also told they could stop the session whenever they wanted with a hand signal to the examiner. Before the start of the recording, baseline state anxiety was assessed with the State-Trait Anxiety Inventory (37). A visual analogue scale for anxiety, which reflects the degree of global subjective anxiety on a continuum from 0 (no anxiety) to 100 (the worst anxiety imaginable), was administered immediately before the recording session, 10 minutes after the beginning, and at the end.

During the whole procedure, the examiner (D.C. or G.M.) monitored on a computer screen the continuous recording of the respiratory parameters breath by breath and interacted with the subjects only at standardized time intervals to administer the psychometric scales. Any disturbances that could modify the respiratory pattern, such as coughs, sneezes, or laughs, were noted by the examiner directly in the data file during the continuous recording, without interrupting the test.

Assessment of respiratory physiology. Respiratory physiology was assessed by the following parameters: respiratory rate, tidal volume, minute ventilation, tidal volume divided by time in inspiration, end-tidal partial pressure of CO₂ (P_{CO₂}), minute ventilation divided by P_{CO₂}, and minute ventilation divided by end-tidal partial pressure of oxygen (P_{O₂}). Tidal volume divided by time in inspiration, minute ventilation divided by P_{CO₂}, and minute ventilation divided by P_{O₂} are believed to reflect the CNS inspiratory drive and chemosensitivity to CO₂ and O₂, respectively (32, 38). For each respiratory parameter we calculated the mean, the average within-subject standard deviation, which is an indicator of the variability of the measure, and the approximate entropy index, which is an indicator of the irregularity and the "disorder" of the measure (14). Data from the first 3 minutes of recording were discarded in order to minimize the influence that familiarization with the face mask and study apparatus could have on the respiratory pattern. Likewise, distortions during the breath-by-breath recording due to artifacts, such as coughs, sneezes, or laughs, were discarded.

Assessment of sighs. We assessed the number of sighs in the breathing pattern. We defined a sigh as any breath that was at least 500 ml larger than the mean of the prior three breaths and at least 400 ml larger than the following breath, according to the definition used by Abelson and co-workers (11). When there were three or more successive such breaths, they were considered a hyperventilatory run and not counted as a sigh (11).

Statistical Analysis

Approximate entropy index. To quantify the irregularity of each time series, we used the approximate entropy index, a model-independent statistic whose mathematical properties and biological applications have been described elsewhere (14, 22). Briefly, the approximate entropy index is a nonnegative number assigned to a time series, with larger values corresponding to greater apparent irregularity in the process and smaller values corresponding to more instances of recognizable patterns in the data. Two input parameters, *m* and *r*, must be specified to com-

TABLE 1. Demographic and Epidemiological Characteristics of Patients With Panic Disorder and Healthy Comparison Subjects

Characteristic	Patients With Panic Disorder (N=40)				Healthy Subjects (N=31)			
	Mean	SD	N	%	Mean	SD	N	%
Age (years)	34.2	11.6			33.0	8.2		
Female			21	53			16	52
Weight (kg)	63.9	12.1			68.9	11.6		
Height (m)	1.7	0.1			1.7	0.1		
Body mass index (kg/m ²)	22.2	3.0			23.1	2.9		
Smoker ^a			23	58			9	29
Sports activity								
Subjects regularly practicing sports			14	35			17	55
Hours per week	1.7	3.9			1.5	1.9		

^a Significant difference between groups ($\chi^2=5.72$, $df=1$, $p<0.05$).

pute approximate entropy: m measures the "length" of a sequence of contiguous observations (a run), and r measures the amount of noise in the data that is filtered out in the ensuing calculation. Approximate entropy measures the likelihood that runs that are close (within r) for m observations remain close (within the same tolerance width r) when m is incremented. A greater likelihood of remaining close (high regularity) produces smaller approximate entropy values, and conversely, random data (high irregularity) produce higher values. In this study, we calculated approximate entropy (m , r) values for all data sets by using $m=1$ and $r=20\%$ of the standard deviation of the individual subject's time series. Normalizing r to each time series' standard deviation gives approximate entropy invariance to translation and scale. Computational aspects have been described in detail by Pincus (39). Previous studies that included both theoretical analysis and clinical applications (22, 40) have demonstrated that these input conditions produce good statistical validity (reproducibility) for approximate entropy applied to time series of the lengths considered here. We analyzed 17 minutes of recording with a sampling rate of one sample every 5 seconds and a typical sequence of data of approximately 200 data points.

Average within-subject standard deviation. To quantify the overall variability of each measured parameter, we used the average within-subject standard deviation. The standard deviation measures the magnitude of the deviation from the mean value for each parameter in each subject.

In summary, standard deviations and approximate entropy values quantify two different characteristics of time series data and provide complementary information. Standard deviations describe the overall variability of a parameter over a period of time, whereas approximate entropy describes the dynamic pattern of that variability. For instance, tracings of a physiologic parameter with similar overall variability (standard deviations) might differ in dynamic patterns; each could have either a regular pattern over time (low approximate entropy), indicating low complexity of the system, or an irregular pattern (high approximate entropy), indicating greater complexity of the system (41).

Data analyses. Parametric statistical analyses were employed. The continuous data were analyzed by t test, analysis of variance (ANOVA), and multivariate analysis of covariance (MANCOVA). The nominal data were compared by chi-square analysis. The correlation between variables was tested by using the Pearson correlation coefficient.

Results

For the patients with panic disorder, the mean illness duration was 7.1 years ($SD=7.9$). Twenty-eight patients (70%) were agoraphobic. The mean total score on the Panic-Associated Symptom Scale was 7.0 ($SD=4.1$), and

the mean scores on the panic attack, anticipatory anxiety, and agoraphobia subscales were 3.5 ($SD=2.5$), 2.3 ($SD=2.0$), and 0.6 ($SD=0.9$), respectively. The mean total score on the Fear Questionnaire was 45.7 ($SD=24.5$), and the mean scores on the agoraphobia, blood-injury phobia, and social phobia subscales were 14.7 ($SD=12.8$), 18.8 ($SD=12.0$), and 12.2 ($SD=8.1$), respectively.

There were no significant differences between the two groups in gender distribution, age, weight, height, body mass index, number of subjects who regularly practiced sports, and hours of sports activity per week, whereas there were significantly more smokers among the panic disorder patients than among the healthy comparison subjects (Table 1).

ANOVA showed that the patients with panic disorder had significantly higher baseline anxiety levels, as measured by the State-Trait Anxiety Inventory, before assessment of respiratory physiology (mean score=45.6, $SD=11.6$) than the healthy comparison subjects (mean=29.2, $SD=4.1$) ($F=56.8$, $df=1$, 69, $p<0.01$). The mean scores on the visual analogue scale for anxiety before respiratory assessment in the patients with panic disorder and the comparison subjects were 36.5 ($SD=25.3$) and 7.0 ($SD=8.7$), respectively. During assessment they were 31.7 ($SD=27.1$) and 4.1 ($SD=5.6$). After respiratory assessment they were 22.9 ($SD=24.9$) and 2.7 ($SD=4.7$). ANOVA for repeated measures showed significant effects of diagnosis ($F=43.0$, $df=1$, 68, $p<0.01$) and time ($F=8.1$, $df=2$, 138, $p<0.01$) in the visual analogue scale scores, while no significant time-by-diagnosis interaction was found.

Baseline Anxiety

A MANCOVA with the State-Trait Anxiety Inventory score as covariate showed no significant differences in the mean values of any of the respiratory parameters between the patients with panic disorder and the healthy comparison subjects. The mean respiratory rates were 16.53 ($SD=4.04$) and 16.33 ($SD=3.72$) breaths/minute, respectively; the mean tidal volumes were 0.55 ($SD=0.20$) and 0.51 ($SD=0.17$) liter; the mean minute ventilations were 8.53 ($SD=2.98$) and 7.87 ($SD=2.13$) liters/min; the mean ratios of tidal volume to time in inspiration were 0.38 ($SD=0.13$) and 0.34 ($SD=0.10$); the mean P_{CO_2} values were 32.43 ($SD=$

TABLE 2. Within-Subject Standard Deviations of Respiratory Parameters for Patients With Panic Disorder and Healthy Comparison Subjects

Respiratory Parameter	Within-Subject Standard Deviation				Post Hoc Duncan Analysis (p)
	Patients With Panic Disorder (N=40)		Healthy Comparison Subjects (N=31)		
	Mean	SD	Mean	SD	
Respiratory rate	2.73	1.35	2.12	0.80	<0.05
Tidal volume	0.19	0.13	0.11	0.05	<0.01
Minute ventilation	2.13	1.40	1.30	0.51	<0.01
Inspiratory drive (tidal volume/time in inspiration)	0.12	0.14	0.06	0.02	<0.05
End-tidal CO ₂ partial pressure (P _{CO₂})	1.83	0.90	1.07	0.30	<0.01
Index of CO ₂ chemosensitivity (minute ventilation/P _{CO₂})	0.08	0.10	0.05	0.06	0.09
Index of O ₂ chemosensitivity (minute ventilation/P _{O₂})	0.02	0.02	0.01	0.01	<0.05

4.60) and 32.89 (SD=3.07) mm Hg; the mean ratios of minute ventilation to P_{CO₂} were 0.27 (SD=0.16) and 0.24 (SD=0.07); and the mean ratios of minute ventilation to P_{O₂} were 0.08 (SD=0.03) and 0.07 (SD=0.02). However, significantly higher average within-subject standard deviations were observed in the patients with panic disorder than in the comparison subjects ($R=3.2$, $df=7$, 62 , $p<0.01$). Post hoc Duncan comparisons showed significantly higher standard deviations in the patients with panic disorder for all respiratory parameters except the ratio of minute ventilation to P_{CO₂} (Table 2).

A MANCOVA with the State-Trait Anxiety Inventory score as covariate showed significantly higher approximate entropy indexes of the baseline respiratory parameters in the patients than in the comparison subjects ($R=2.6$, $df=7$, 62 , $p<0.02$). Post hoc Duncan comparisons showed significantly higher indexes in the patients with panic disorder than in the healthy comparison subjects for all respiratory parameters (Table 3).

Similar results were obtained when the score on the visual analogue scale for anxiety before respiratory assessment was included as a covariate in the MANCOVA (data available on request).

Gender

A MANCOVA with the State-Trait Anxiety Inventory as a covariate and diagnosis and gender as grouping factors showed significant gender effects for the mean values of the respiratory parameters ($R=6.0$, $df=7$, 60 , $p<0.01$), whereas no significant diagnosis effect or diagnosis-by-gender interaction was found. The male subjects showed significantly higher mean values for tidal volume, minute ventilation, tidal volume/time in inspiration, P_{CO₂}, and minute ventilation/P_{O₂} than the female subjects (post hoc Duncan comparisons, $p<0.01$ for all measures), whereas the mean values for respiratory rate and minute ventilation/P_{CO₂} were not significantly different (data available on request). A MANCOVA with the State-Trait Anxiety Inventory score as a covariate and diagnosis and gender as grouping factors showed a diagnosis effect for the standard deviations ($R=3.0$, $df=7$, 60 , $p<0.01$) and approximate entropy indexes ($R=2.5$, $df=7$, 60 , $p<0.05$) but did not show either a significant gender effect or a diagnosis-by-gender

interaction for the standard deviations or approximate entropy indexes of any respiratory parameter.

Smoking

A MANCOVA with the State-Trait Anxiety Inventory as covariate and diagnosis and smoking as grouping factors showed a significant diagnosis effect for the standard deviations ($R=2.5$, $df=7$, 60 , $p<0.05$) and approximate entropy indexes ($R=2.2$, $df=7$, 60 , $p<0.05$) but not for the mean values of the respiratory parameters. No significant effect of smoking on the mean values, standard deviations, or approximate entropy indexes for any respiratory parameter was found. No significant diagnosis-by-smoking interaction was found for the mean values or approximate entropy indexes of any respiratory parameter, whereas a significant effect on the standard deviations was found ($R=2.5$, $df=7$, 60 , $p<0.05$). Post hoc Duncan comparisons showed higher standard deviations in smoking patients with panic disorder than in smoking comparison subjects for respiratory rate (mean=3.08, SD=1.58, and mean=1.63, SD=0.48, respectively) ($p<0.01$), tidal volume (mean=0.18, SD=1.11, and mean=0.01, SD=0.05, respectively) ($p<0.05$), minute ventilation (mean=2.27, SD=1.37, and mean=1.17, SD=0.41, respectively) ($p<0.01$), P_{CO₂} (mean=1.94, SD=0.91, and mean=1.17, SD=0.44, respectively) ($p<0.01$), minute ventilation/P_{O₂} (mean=0.03, SD=0.03, and mean=0.01, SD=0.00, respectively) ($p<0.05$), and tidal volume/time in inspiration (mean=0.10, SD=0.07, and mean=0.05, SD=0.02, respectively) ($p<0.01$).

Sports

A MANCOVA with the State-Trait Anxiety Inventory score as covariate and diagnosis and sports as grouping factors showed a significant diagnosis effect for the standard deviations ($R=3.4$, $df=7$, 60 , $p<0.05$) and approximate entropy indexes ($R=2.3$, $df=7$, 60 , $p<0.05$) but not for the mean values of the respiratory parameters. No significant sports effect or diagnosis-by-sports interaction for mean values, standard deviations, or approximate entropy indexes of any respiratory parameter was found.

Clinical Characteristics

Linear Pearson correlation did not show any significant correlation between the approximate entropy index of any

TABLE 3. Approximate Entropy Indexes of Respiratory Parameters for Patients With Panic Disorder and Healthy Comparison Subjects

Respiratory Parameter	Approximate Entropy Index ^a						Post Hoc Duncan Analysis (p)	
	Patients With Panic Disorder				Healthy Comparison Subjects (N=31)		All Patients Versus Comparison Subjects	Patients Without Sighs Versus Comparison Subjects
	Total (N=40)		Without Sighs (N=19)		Mean	SD		
Respiratory rate	1.44	0.26	1.27	0.18	1.13	0.20	<0.01	<0.01
Tidal volume	1.31	0.21	1.37	0.21	1.11	0.19	<0.01	<0.01
Minute ventilation	1.44	0.22	1.32	0.13	1.29	0.13	<0.01	0.52
Inspiratory drive (tidal volume/time in inspiration)	1.41	0.22	1.30	0.13	1.27	0.17	<0.01	0.62
End-tidal CO ₂ partial pressure (Pco ₂)	1.38	0.33	1.22	0.31	1.09	0.20	<0.01	0.07
Index of CO ₂ chemosensitivity (minute ventilation/Pco ₂)	1.40	0.23	1.27	0.12	1.23	0.16	<0.01	0.45
Index of O ₂ chemosensitivity (minute ventilation/PO ₂)	1.47	0.22	1.35	0.11	1.31	0.13	<0.01	0.43

^a Larger values correspond to greater apparent irregularity in the process.

respiratory parameter and illness duration or severity of clinical symptoms, measured by the global and subscale scores on the Panic-Associated Symptom Scale and the Fear Questionnaire.

Sighs

A *t* test showed a higher number of sighs by the patients with panic disorder than by the healthy comparison subjects (mean=4.6, SD=6.8, and 0, respectively) ($t=3.8$, $df=69$, $p<0.01$). Twenty-one patients (53%) with panic disorder made sighs, whereas 19 (48%) did not. None of the healthy subjects had sighs in their breathing patterns. There were no significant differences in gender distribution, age, weight, height, body mass index, number of subjects who regularly practiced sports, hours of sports activity per week, illness duration, or severity of clinical symptoms between the patients with sighs and without sighs.

We compared the mean values, standard deviations, and approximate entropy indexes for all respiratory parameters in the patients with sighs, patients without sighs, and comparison subjects. A MANCOVA with the State-Trait Anxiety Inventory score as covariate showed no significant difference in the mean values of any respiratory parameter among the three groups. A MANCOVA with the State-Trait Anxiety Inventory score as covariate showed a significant group effect for the standard deviations ($R=6.7$, $df=14$, 122 , $p<0.01$). Post hoc Duncan comparisons showed higher standard deviations in the patients with sighs than in the comparison subjects for all respiratory parameters ($p<0.01$), higher standard deviations in the patients with sighs than in patients without sighs for respiratory rate, tidal volume, minute ventilation, and Pco₂ ($p<0.01$), but no difference between the patients without sighs and comparison subjects in any respiratory parameter (data available on request).

A MANCOVA with the State-Trait Anxiety Inventory score as covariate showed a significant group effect for the approximate entropy indexes ($R=4.4$, $df=14$, 122 , $p<0.01$). Post hoc Duncan comparisons showed higher approxi-

mate entropy indexes in the patients with sighs than in the comparison subjects for all respiratory parameters ($p<0.01$), higher indexes in the patients with sighs than in the patients without sighs for respiratory rate (mean=1.62, SD=0.16, and mean=1.27, SD=0.18, respectively) ($p<0.01$), minute ventilation (mean=1.59, SD=0.17, and mean=1.32, SD=0.13) ($p<0.01$), Pco₂ (mean=1.58, SD=0.16, and mean=1.22, SD=0.31) ($p<0.01$), minute ventilation/PO₂ (mean=1.62, SD=0.16, and mean=1.35, SD=0.11) ($p<0.01$), minute ventilation/Pco₂ (mean=1.55, SD=0.18, and mean=1.27, SD=0.12) ($p<0.01$), and tidal volume/time in inspiration (mean=1.54, SD=0.18, and mean=1.30, SD=0.13) ($p<0.01$), and higher indexes in the patients without sighs than in the comparison subjects for respiratory rate and tidal volume (Table 3). Similar results were obtained by defining a sigh as 2.0 times the mean tidal volume, according to the definition used by Wilhelm and co-workers (13) (data available on request).

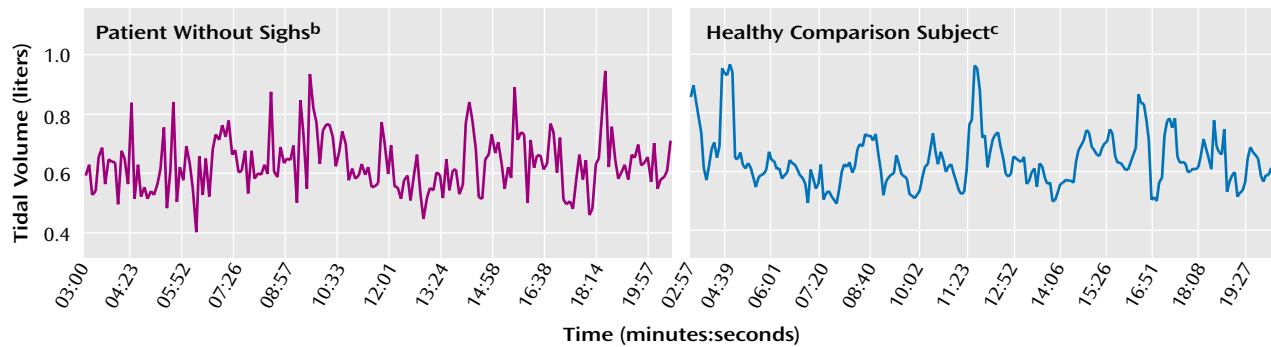
In the patients with sighs, the linear Pearson correlation did not show any significant correlation between the approximate entropy index for any respiratory parameter and the number of sighs.

None of the tested subjects experienced panic attacks or asked to stop the recording during assessment of respiratory physiology.

Discussion

The main finding of our study is that patients with panic disorder had significantly higher approximate entropy indexes and higher average within-subject standard deviations than healthy comparison subjects for the measured respiratory parameters, whereas the mean values did not discriminate between the two groups. Our findings suggest that patients with panic disorder have not only greater overall variability but also greater entropy in baseline respiratory patterns, indicating greater irregularity and complexity in their respiratory functioning. This is in agreement with recent findings of higher values for ap-

FIGURE 1. Breathing Patterns With Similar Overall Variability (Standard Deviations) and Significantly Different Approximate Entropy Indexes^a in a Patient With Panic Disorder Who Did Not Sigh During Testing and a Healthy Comparison Subject



^a Larger values correspond to greater apparent irregularity in the process.

^b SD=0.09, approximate entropy index=1.65.

^c SD=0.09, approximate entropy index=1.21.

proximate entropy and the largest Lyapunov exponent, a measure of chaos, for lung volume in patients with panic disorder than in normal subjects (27).

Baseline anxiety was greater in the patients than in the comparison subjects but was not able to explain our respiratory findings. Moreover, the scores on the visual analogue scale for anxiety during the procedure decreased similarly in the two groups, indicating that the procedure was no more anxiogenic for the patients than for the comparison subjects. Severity of illness did not influence the irregularity of the respiratory pattern either. Other variables that could influence respiratory pattern, i.e., age, weight, height, and body mass index, did not differ between the patients and comparison subjects.

The male subjects had higher mean values of some respiratory measures than the female subjects, as expected from the physiological difference in body mass (32), whereas no differences were found for respiratory patterns. Sports activity did not influence the measured respiratory parameters. As in epidemiological studies (42), smokers were more prevalent among the patients with panic disorder than among the comparison subjects. The smoking patients with panic disorder had greater variability in some respiratory parameters than smoking comparison subjects, but they did not differ on the irregularity of their breathing patterns. In brief, the main somatic and individual variables related to respiration are unable to explain the difference in respiratory pattern found.

Approximate Entropy and Sighs

Our findings do not completely overlap with those of studies that showed greater irregularity of tidal volume due to frequent sighs in patients with panic disorder (8, 10, 11, 13). In our study, the patients with panic disorder showed significantly more sighs than the healthy subjects, but the presence of sighs does not fully explain the irregularity in breathing patterns. Although the patients with sighs showed higher approximate entropy indexes for the respiratory parameters, except for tidal volume,

than the patients without sighs, the latter showed significantly higher indexes for respiratory rate and tidal volume than the healthy subjects. These findings suggest that sighs contribute to the irregularity of breathing patterns but do not account for all of the differences in approximate entropy between patients with panic disorder and healthy subjects. At least for the two main respiratory parameters, respiratory rate and tidal volume, the irregularity of breathing patterns in patients with panic disorder is not attributable to the presence of sighs. Moreover, the lack of correlation between the approximate entropy index for any respiratory parameter and the number of sighs supports the possibility that sighs do not fully explain the irregularity of the patterns for the other respiratory parameters.

Unlike the approximate entropy indexes, the standard deviations for all the respiratory parameters did not differ between the patients without sighs and the comparison subjects. This finding confirms that a linear measure of variability is unable to fully discriminate between patients and healthy subjects for a highly complex function such as respiration, whereas a nonlinear measure does so (Figure 1).

The role of sighs in patients with panic disorder is unclear. Since the sighs have a physiological function in maintaining normal lung volumes and reducing unpleasant respiratory sensations (43), they could be a mechanism that compensates for the abnormal respiratory functioning of patients with panic disorder. Alternatively, the sighs could be an expression of greater abnormality in the functioning of the rhythm-generating respiratory network (see the following). Further studies are necessary to clarify these issues.

Implications of Approximate Entropy for Pathophysiology of Panic Disorder

Entropy characterizes the amount of randomness or disorder in processes and systems. Living organisms have been described as highly complex and dynamic structures

that display a meta-equilibrium around homeostatic levels, oscillating between order and disorder (44, 45). External or internal perturbations can lead a biological system to a state with a high degree of instability, defined as a “bifurcation point,” from which the system may proceed to diverging states, such as a new level of order or, on the contrary, to a “disruption,” such as a pathological phenomenon (46). The greater entropy in the respiratory functioning of patients with panic disorder may indicate an intrinsic instability state in respiratory homeostasis on which different critical inputs could act as “disrupting” factors leading to panic attacks. Respiratory instability may underlie the susceptibility of patients with panic disorder to hypercapnic challenges (1).

The question of whether greater respiratory entropy could be a consequence of panic disorder or a trait marker of vulnerability to panic disorder is open, but two studies support the latter hypothesis. Coryell and co-workers (47) reported abnormal respiratory patterns in healthy first-degree relatives of patients with panic disorder breathing a 5% CO₂ gas mixture. Preliminary data from our team (48) showed greater approximate entropy in the baseline respiratory patterns of healthy children of patients with panic disorder than in the children of healthy subjects. Instability in respiratory systems might lead to the onset of the disease when the system fails to cope with the stimuli and fails to restore the state of equilibrium. Daily tobacco smoking increases the risk for onset of panic attacks and disorder (42). Since nicotine seems to modulate neurotransmission in the respiratory brainstem network (49), an intrinsic respiratory instability might underlie the development of the disorder after the onset of smoking.

The source of greater respiratory entropy in patients with panic disorder is unclear. Respiration is modulated by a complex regulatory system in which the brainstem plays a central role in containing the pacemaker respiratory neurons and the neural network that shape respiratory patterns (50). Irregularity in breathing patterns might arise from abnormal functioning of the rhythm-generating network, leading to a lack of physiological synchronicity in inspiratory and expiratory neuron activity. Since limbic and cortical areas influence respiration (51, 52), physiological instability could also originate from brain centers higher than the brainstem. However, the role of higher centers is called into question by the absence of an influence of state anxiety on respiration instability and by the reported lack of influence of cognitive manipulation on doxapram-induced irregularity in tidal volume in patients with panic disorder (11).

The greater respiratory irregularity might also influence the heart rate of patients with panic disorder. Several studies have demonstrated less variability in heart rate in patients with panic disorder (53–55), and one study has shown less chaos in a heart rate time series (56). Since cardiac activity is regulated by direct connections between respiratory and sympathetic/vagal cardiac centers within the

brainstem, abnormal functioning of the respiratory network could affect the autonomic regulation of cardiac activity, leading to abnormal modulation of the heart rate.

Finally, the greater respiratory entropy in patients with panic disorder does not necessarily imply a specific intrinsic instability in the respiratory system, but it might arise from a more global abnormality in the brainstem neuronal circuits regulating physiological homeostasis functions (57). This idea is supported by the observation that patients with panic disorder show subclinical abnormalities in the functioning of the balance system (58).

In conclusion, this study shows greater irregularity and complexity in the respiratory functioning of patients with panic disorder. This finding supports the idea of abnormal regulation of the respiratory system as a key mechanism in panic disorder. Greater respiratory entropy could represent a vulnerability factor for panic attacks. Further studies are necessary to confirm the specificity of the results, comparing patients with panic disorder and patients with other anxiety disorders. Identification by brain imaging of specific brain structures related to this abnormal respiration feature could help to build a much-needed neuroanatomical model of “respiratory” panic.

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