Physiologic Instability in Panic Disorder and Generalized Anxiety Disorder

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Background: *Because panic attacks can be accompanied by surges in physiologic activation, we tested the hypothesis that panic disorder is characterized by fluctuations of physiologic variables in the absence of external triggers.*

Methods: *Sixteen patients with panic disorder, 15 with generalized anxiety disorder, and 19 normal control subjects were asked to sit quietly for 30 min. Electrodermal, cardiovascular, and respiratory measures were analyzed using complex demodulation to quantify variability in physiologic indices.*

Results: *Both patient groups reported equally more anxiety and cardiac symptoms than control subjects, but certain other somatic symptoms, including breathlessness, were elevated only in panic disorder patients. Mean end-tidal pCO_2 and respiratory rates were lower, and tidal volume and the number of sighs were higher in panic disorder patients than control subjects. Neither cardiovascular (heart rate, arterial pressure, cardiac output), nor electrodermal instability including sighs distinguished the groups; however, tidal volume instability was greater in panic disorder than generalized anxiety disorder patients or control subjects. Several other respiratory measures (pCO_2, respiratory rate, minute volume, duty cycle) showed greater instability in both patient groups than in control subjects.*

Conclusions: *Respiration is particularly unstable in panic disorder, underlining the importance of respiratory physiology in understanding this disorder. Whether our findings represent state or trait characteristics is discussed.*
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Key Words: Anxiety disorders, panic attacks, respiration, autonomic nervous system, arousal, stroke volume

Introduction

Panic attacks occur unexpectedly in panic disorder (PD), apparently independent from external events. Biological observations of natural panic attacks have been thwarted by the infrequency of such attacks, which often occur less than daily: capturing one when a patient is being physiologically monitored is difficult. Provocation of panic attacks in the laboratory by artificial means like lactate infusion (Liebowitz et al 1984, 1985) or carbon dioxide inhalation (Gorman et al 1994) is limited by the fact that we cannot be certain that induced attacks are identical with natural ones, either in physiologic characteristics or in mechanism. An alternative is to search for biological features that might underlie the susceptibility of patients with current panic disorder to attacks. Such features may be present more or less continuously, not just during attacks, being markers for PD as a "trait" rather than panic attacks as a "state." In other psychiatric disorders, such features have been called "endophenotypical" (Lenzenweger 1999) because they are more hidden than phenotypic clinical symptoms.

A logical starting point is to look for fluctuations in biological features known to be associated with full-blown attacks but fluctuations of smaller magnitude, perhaps below the subject's threshold for noticing them at all. Such features might reveal an instability that could on occasion escape its usual inhibitory mechanisms, analogous to the interictal electroencephalographic spikes present in certain epileptic patients. In PD, however, activity of autonomic nervous or respiratory systems is likely to be especially relevant. The cardiovascular system is a reasonable candidate because heart rate is a leading index of clinical anxiety in certain situations (Wilhelm and Roth 1998). The respiratory system is another because it has connections to panic through the suffocation false alarm hypothesis of Klein (1992) and observations of the hyperventilation syndrome (Ley 1985). Increased respiratory variability has been reported in PD at times when no clinical panic attacks were being provoked (Abelson et al 1996; Bystritsky and Shapiro 1992; Gorman et al 1988; Schwartz et al 1996; Stein et al 1995). To these systems should be added the electrodermal system, which along with heart

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Table 1. Description of Groups: Mean (SD)

	PD	GAD	Control subjects	F, H, or χ^{2a}	p	Post hoc
Description of groups						
Number in sample	16	15	19			
Women (%)	68.8	60.0	63.2	$\chi^2 = 0.87$	—	
Age (years)	44.0 (9.0)	37.3 (9.0)	43.7 (16.1)	1.53	—	
Beck Depression Inventory	7.27 (5.80)	5.18 (2.32)	1.88 (2.39)	8.32	.0009	P > C
STAI-Trait	47.0 (8.5)	44.1 (8.3)	32.4 (9.0)	12.50	.0001	P = G > C
Body Sensations Questionnaire	2.64 (0.97)	2.39 (0.77)	1.36 (0.33)	5.93	.005	P > C
Agoraphobic Cognitions Questionnaire	2.23 (0.60)	1.79 (0.59)	1.68 (0.73)	11.80	.0001	P > C
Mobility Inventory (unaccompanied)	2.64 (0.94)	1.33 (0.32)	1.41 (0.38)	19.23	.0001	P > G = C
SCL-90-R general severity index (*t*)	65.4 (9.7)	64.7 (7.6)	46.9 (13.2)	15.69	.0001	P = G > C
Shortness of breath when anxious						
How often? (1–4)[b]	3.50 (0.73)	2.33 (1.18)	1.58 (0.84)	$H = 23.17$	.0001	P > G > C
Fear shortness of breath? (1–4)[c]	3.13 (1.15)	1.73 (0.96)	1.32 (0.58)	$H = 18.66$	.0001	P > G = C

PD, panic disorder; GAD, generalized anxiety disorder; STAI, State-Trait Anxiety Inventory; SCL, Symptom Check List.

[a] F ratios from one-way analyses of variance (ANOVAs) (df = 2,47), followed by Tukey Honestly Significant Difference pairwise post hoc comparisons; H ratios from Kruskal-Wallis ANOVAs by ranks, followed by Mann-Whitney U-tests; χ^2 from contingency tables.

[b] 1–4, never/seldom/sometimes/often.

[c] 1–4, not at all/slightly/moderately/extremely.

rate was recently found to be more unstable in PD patients than in comparison groups (Roth et al 1998a). Not much is known about the stability of hemodynamic measures such as arterial pressure, stroke volume, or cardiac output in PD patients.

In the study reported here, we compared PD patients to nonanxious volunteers and to generalized anxiety disorder (GAD) patients during a 30-min period of quiet sitting. Inclusion of an additional anxiety diagnosis permits tests of the diagnostic specificity of any findings. Generalized anxiety disorder patients are conceived of having more sustained anxiety than PD patients, accompanied by persistent worried thoughts. This anxiety may not be reflected in heightened autonomic activation (Hoehn-Saric et al 1989). We hypothesized that compared to GAD patients and control subjects, PD patients would have less stable cardiovascular, electrodermal, and respiratory systems due to fluctuations or surges in autonomic activation and/or respiratory regulation. We use the term "stable" descriptively as an opposite of "variable" or "fluctuating," without specific implications for what homeostatic or heterostatic mechanisms might be involved. Stability was determined by complex demodulation, and in the case of tidal volume, additionally by calculating coefficients of variation and root mean squared successive differences (rMSSD).

Ten minutes before beginning this quiet sitting period, subjects had completed a procedure where they had held their breath for 30 sec 12 times at 60-sec intervals (Roth et al 1998b). A main result of this study was that increases in self-rated anxiety during breath holding were not different in the three groups. Although the self-rated anxiety for the PD, GAD, and control groups did not change significantly from before to after the breath-holding procedure, end-tidal pCO_2 became significantly lower for PD patients than control subjects.

Methods and Materials

Subjects

Sixteen patients with PD, 15 with GAD, and 19 psychiatrically healthy control subjects were recruited by advertisement. Patients were candidates for clinical drug trials and were not paid for their participation, whereas control subjects were. Advertisements for control subjects asked for volunteers not suffering from excessive anxiety or stress. Diagnosis of patients and exclusion of anxiety disorders and other Axis I disorders in control subjects was made by the Structured Clinical Interview for DSM-III-R (American Psychiatric Association 1987). Eligible subjects signed a consent form before participation. Three of the GAD patients had a history of PD, but their PD was in full remission and they had no agoraphobia. Three of the PD patients had a secondary diagnosis of GAD. Two of the PD patients, two of the GAD patients, and one of the normal control subjects had a history of a major depressive episode, but none was having such an episode at the time of testing. On the basis of the structured interview, four of the PD patients qualified for the respiratory subtype of Briggs et al (1993). All patients and normal control subjects denied taking psychoactive or cardiovascularly active medication in the 2 weeks before testing, although this was not verified by drug screens. None of the subjects reported current epileptic, respiratory, or cardiovascular disease. As noted in Table 1, groups were successfully selected not to differ significantly in age or in the proportion of women.

Prior to testing, subjects filled out several questionnaires including the Beck Depression Inventory (Beck et al 1961), the State-Trait Anxiety Inventory (STAI) (Spielberger et al 1970), the Body Sensations Questionnaire (Chambless et al 1984), the

Agoraphobic Cognitions Questionnaire (Chambless et al 1984), the Symptom Check List-90, revised (SCL-90-R) (Derogatis 1977), and the Mobility Inventory (Chambless et al 1985), which assesses difficulty in entering typical agoraphobic situations. In addition, subjects filled out a Respiration Questionnaire, devised by the authors (Roth et al 1998b). Table 1 shows that on all questionnaires the scores for PD patients were significantly greater than for control subjects, with GAD patients tending to be intermediate. STAI-Trait anxiety and SCL-90-R general severity were about equal in both patient groups, and greater than in control subjects. Panic disorder patients had more restricted mobility than GAD patients, and experienced and feared shortness of breath more.

Procedure

Subjects sat upright in a comfortable chair in a large, quiet, temperature-controlled room. They were instructed to sit quietly for the next 30 min and to avoid moving in the chair because that could interfere with the recordings. They were to keep their mouth sealed and breathe only through their nose so that the nasal prongs could sample the air they breathed in and out. In addition, they were to keep their eyes open. There was no mention in the instructions that anxiety or panic attacks might occur during the procedure, nor provisions made for its premature termination.

Self-Report Measures

Subjects filled out questionnaires at two points in time, immediately prior to and following the quiet sitting. Before the quiet sitting, they rated their subjective anxiety using a Subjective Unit of Distress (SUD) scale ranging from 0 (not at all) to 10 (extremely strong). Then they filled out a STAI-State Form (20 items rated 1–4 allow a maximum score of 80). Following the quiet sitting, they reported their SUD anxiety two more times, once for their current anxiety and once retrospectively for their maximum anxiety while sitting. Then they filled out a Symptom Questionnaire A retrospectively for the same period. It listed the 13 DSM-III-R symptoms with "heart racing, pounding, or skipping" combined with "chest pain or pressure" to give a total of 12 items. Subjects rated each item on a 5-point scale from 0 (not at all) to 4 (to a high degree). The last item on this questionnaire asked if subjects had had "attacks during the test when you suddenly felt more frightened, anxious, or extremely uncomfortable," and how many such attacks they had had. If they answered yes, subjects were asked to fill out Symptom Questionnaire B for this episode (or the worst episode), which was a list of the 13 symptoms comprising the diagnostic criteria for a panic attack in the Diagnostic and Statistical Manual of Mental Disorders (Third Edition-Revised or DSM-III-R), following each one of which subjects circled "yes" or "no."

Subjects were considered *panickers* if they endorsed having had an attack during the quiet sitting period and four or more symptoms, at least one of which was cognitive (fear of dying, going crazy, or losing control). In addition, they had to give an SUD anxiety rating higher than their rating given before that period (cf Sanderson et al 1989).

Physiologic Measures

Recordings of several physiologic channels were made at the Laboratory of Clinical Psychopharmacology and Psychophysiology with the Vitaport I System (Meditec, Karlsruhe, Germany).

1. Skin conductance (SC) level was recorded from digits 3 and 4 of the left hand. Nonspecific SC fluctuations were detected as previously described (Roth et al 1998a).
2. From an electrocardiogram lead, R-R intervals were measured and instantaneous heart rate was calculated. Values from ectopic or other kinds of abnormal beats were deleted and replaced by linearly interpolated values.
3. The continuous arterial blood pressure waveform was taken from the index finger of the nondominant hand by means of the Finapres 2300 (Ohmeda, Madison, WI) system. With this device, we are able to measure beat-to-beat systolic and diastolic blood pressure and estimate stroke volume, cardiac output, and systemic vascular resistance using pulse contour analysis. These measurements have been previously validated (Gratz et al 1992; Imholz et al 1990; Stok et al 1993). Editing of abnormal beats was done as in number 2 above.
4. Two channels of respiration were measured with inductive plethysmography using Respibands (Respitrace Corporation, Ardsley, NY) placed around the chest and abdomen. This method is the least intrusive for measuring respiratory volumes; measurement methods requiring a facemask or mouthpiece are known to alter natural breathing (Askanazi et al 1980). Calibration against spirometry was accomplished by the least-squares method (Morel et al 1983). Eighty-nine percent of the tidal volumes measured by this method have been shown to be within $\pm$10% of simultaneous spirometric measurements, and 100% within $\pm$20% (Tobin et al 1987). Breaths containing artifacts (due to cough, movement, etc.), which were generally less than 1% of breaths, were identified by visual inspection of respiration in the two channels. Parameters derived from these distorted breaths were replaced by values interpolated from adjacent breaths. Several respiratory parameters were calculated breath-by-breath using customized programs (Wilhelm et al 1999): instantaneous respiratory rate, tidal volume, minute ventilation, mean inspiratory flow rate (a putative measure of respiratory drive), and duty cycle (ratio of inspiratory time to total breath duration, a measure of the timing of the respiratory on/off switch) (Milic-Emili 1982). Following convention, sighs were defined as tidal volumes exceeding 200% of the individual's average. Apneas were defined as intervals where breathing was suspended for more than 5 sec.
5. Expiratory pCO_2 was measured continuously by a calibrated infrared capnograph (Datex B, Puritan-Bennett Corporation, San Ramon, CA) into which air was drawn with a flow rate of 150 mL/min through a 1.2 mm diameter plastic tube ending in a dual nostril prong. Subjects were instructed to breathe only through their nose. End-tidal pCO_2 was determined as the level at which pCO_2 stopped rising at the end of an expiration (final maximum). Expirations with a low percentage of alveolar air can be

recognized by the pCO_2 waveform not reaching a plateau (Bass and Gardner 1985), and these were deleted and replaced by linearly interpolated values in a small percentage of breaths.

Variability Indices

For the assessment of beat-to-beat (for 2 and 3) or breath-to-breath (for 4 and 5) within-subject variability (instability), values for each beat or breath were converted into equidistant time series using cubic spline interpolation and resampling at 4 Hz. Our main assessment of variability was to apply complex demodulation to these time series, with a bandpass of 0.004–0.14 Hz (corresponding to period lengths of 6.6–240 sec) and a transition band widths of 0.033 Hz. This nonlinear time-domain method of time series analysis was developed for quantifying nonstationary oscillations in defined frequency ranges (Bloomfield 1976). We also calculated rMSSD and coefficients of variation so that we could relate our results for tidal volumes to those in the literature.

To understand the advantages of complex demodulation, consider a variable like tidal volume. The SD or the coefficient of variation (SD divided by the mean) of a sequence of consecutive tidal volumes does not distinguish between the contribution of slow changes over the entire time window and faster changes that might occur, say, between consecutive volumes. A measure like the rMSSD statistic (e.g., Gorman et al 1987) depends only on consecutive volumes and thus indexes only these faster changes; however, "faster" is imprecisely specified since the unit of measurement is a discrete event (a single respiratory cycle) whose time scale depends on the respiration rate in the time window being analyzed. Complex demodulation of tidal volumes that have been expressed as an equidistant time series, on the other hand, is able to quantify stability in defined frequency bands independent of variability in event frequency. Furthermore, complex demodulation in such a time series can be applied in a parallel fashion both to discrete variables such as tidal volume and to continuous variables such as skin conductance level. Finally, unlike spectral analysis, complex demodulation is effective in characterizing nonstationary variability that drifts in frequency and amplitude or occurs in bursts (Hayano et al 1994; Wilhelm et al 1997).

Statistical Analysis

Self-report measures were analyzed either with (1) one-way analyses of variance (ANOVA) with the factor Group (PD patients, GAD patients, control subjects), followed when significant by pairwise comparisons using the Tukey Honestly Significant Difference test for unequal *N*, or (2) nonparametric tests such as the Kruskal-Wallis ANOVA by ranks followed by the Mann-Whitney *U* test. Physiologic measures were analyzed using repeated measures ANOVAs applied to means of three consecutive 10-min segments of the quiet sitting period, segments long enough for reliable estimates of relatively infrequent events like sighs but short enough to detect trends over time. This analysis had the factors Group (PD patients, GAD patients, control subjects) and Time (T1, T2, T3). Group main effects and Group × Time interactions were examined. Significant effects were followed by Tukey's test, with comparison-specific error terms for effects involving the Group and Time factors.

The statistical analyses can be classified into those that test *a priori* hypotheses and those that are exploratory and which because of their number are particularly prone to Type I errors. Our principal hypotheses concerned variability; we expected that PD patients would show more variable tidal volumes, heart rates, and skin conductance levels than the other groups. In a second report (Wilhelm et al 2001), we present a much more detailed analysis of the sighs in this data set and breaths preceding and following them.

Results

Self-Report Measures

Table 2 presents a summary of the self-report data. With respect to anxiety, the two patient groups did not differ from each other, but both were more anxious than control subjects. The same applied to anxiety symptom scores and to the individual item of heart racing, etc. More PD patients were panickers than GAD patients or control subjects. PD patients were also higher than GAD patients on shortness of breath. Sweating and hyperventilation symptoms did not differ between the groups.

Physiologic Measures

Table 3 presents a summary of physiologic data means over the entire 30-min quiet sitting period. None of the electrodermal or cardiovascular measures showed a group effect. Of the respiratory variables, end-tidal pCO_2, respiratory rate, and duty cycle were lower, and tidal volume, inspiratory flow rate, and the number of sighs were higher in PD patients than control subjects. When sighs were removed by substituting for them the individual's mean tidal volume, tidal volume remained greater in PD patients than control subjects. GAD patients had values intermediate between PD patients and control subjects, except for duty cycle. Significant Group × Time interactions were found for only two variables: minute volume [$F(4,94) = 3.57$, $p < .009$], because of a decline for the GAD group over time, whereas the other two groups slightly increased; and inspiratory flow rate [$F(4,94) = 3.56$, $p < .01$], which followed the same pattern. As illustrated in Figure 1, tidal volume, which showed the greatest overall group difference, was quite stable over 10-min time segments.

Table 4 presents a summary of physiologic data variability as determined by complex demodulation with a frequency range of 0.004–0.14 Hz. None of the electrodermal or cardiovascular measures showed group effects, whereas all of the respiratory variables did. Tidal volume variability was higher in PD than in GAD patients or control subjects. GAD patients had variability values

Table 2. Self-Report Data: Mean (SD) and Statistical Comparisons

	PD	GAD	Control subjects	F, H, or χ^{2a}	p	Post hoc
Anxiety						
STAI-State before quiet sitting	43.5 (8.3)	47.3 (12.8)	27.0 (5.5)	23.48	.0001	P = G > C
SUD anxiety before	4.19 (3.12)	5.00 (2.65)	0.63 (1.07)	16.81	.0001	P = G > C
SUD anxiety after	4.31 (4.00)	4.60 (3.33)	0.58 (0.84)	10.24	.0001	P = G > C
SUD anxiety maximum during	5.63 (4.06)	5.07 (3.61)	0.95 (1.18)	11.87	.0001	P = G > C
Panic attacks						
Panic attacks ≥4 symptoms	6/16	1/15	0/19	11.12	.004	P > G = C
Symptom Questionnaire A						
Symptom total score	7.81 (8.45)	4.21 (4.30)	2.11 (4.86)	$H = 6.31$	.04	P = G > C
Number of symptoms	3.69 (3.72)	2.36 (2.31)	0.89 (1.29)	$H = 6.39$	.04	P = G > C
Shortness of breath	1.06 (1.12)	0.29 (0.47)	0.00 (0.00)	$H = 15.03$	.006	P > G > C
Heart racing, pounding, skipping, or chest pain or pressure	0.94 (1.34)	0.71 (0.91)	0.11 (0.46)	$H = 8.57$	.01	P = G > C
Sweating	0.38 (0.72)	0.21 (0.58)	0.11 (0.32)	$H = 1.55$	—	
Dizziness, unsteadiness, or faintness	0.56 (1.09)	0.36 (0.63)	0.16 (0.69)	$H = 3.11$	—	
Tingling or numbness	0.81 (1.22)	0.64 (1.28)	0.68 (1.11)	$H = 0.28$	—	

PD, panic disorder; GAD, generalized anxiety disorder; STAI, State-Trait Anxiety Inventory; SUD, Subjective Unit of Distress.
[a] F ratios from one-way analyses of variance (ANOVAs) (df = 2,47), followed by Tukey Honestly Significant Difference pairwise post hoc comparisons; H ratios from Kruskal-Wallis ANOVAs by ranks, followed by Mann-Whitney U-tests; χ^2 from contingency tables.

between PD patients and control subjects, except for duty cycle variability, which was highest in GAD, and respiratory rate. When sighs were removed by substituting for them the individual's mean tidal volume, tidal volume variability remained greater in anxiety patients than control subjects but not in PD compared to GAD. As illustrated in Figure 1, tidal volume variability was stable over 10-min epochs. None of the variability measured showed significant Group × Time interactions. Correlations between tidal volume variability and pCO_2 variability were positive and significant for the pooled subjects [$r(43) = .33$, $p < .03$] and within control subjects [$r(17) = .68$, $p < .003$], but not within PD patients [$r(14) = .05$, $p > .8$] or GAD patients [$r(12) = .13$, $p > .6$]. Correlations between tidal volume variability and pCO_2 level were negative and significant for the pooled subjects [$r(43) = -.34$, $p < .03$], showed a trend toward significance within GAD patients [$r(12) = -.51$, $p < .09$] and control subjects [$r(17) = -.45$, $p < .07$], but was insignificant within PD patients [$r(14) = -.12$, $p > .7$].

Table 3. Physiologic Measures: Means (SD) during 30 Min of Quiet Sitting

	PD	GAD	Control subjects	F^a	p	Post hoc
Electrodermal and cardiovascular						
SC level (μSiemens)	7.80 (6.20)	7.14 (4.61)	4.50 (3.60)	2.14	—	
Nonspecific SC fluctuations (number/min)	3.05 (2.63)	2.87 (2.64)	1.60 (1.64)	2.08	—	
Heart rate (beats/min)	70.1 (8.2)	76.8 (18.2)	69.0 (11.4)	0.88	—	
Systolic blood pressure (mm Hg)	144.4 (31.5)	152.2 (33.1)	148.9 (23.1)	0.28	—	
Diastolic blood pressure (mm Hg)	87.4 (25.1)	91.9 (18.7)	90.8 (16.8)	0.21	—	
Stroke volume (mL)	61.5 (22.3)	64.4 (20.0)	60.0 (16.9)	0.21	—	
Cardiac output (L/min)	4.31 (1.40)	4.95 (1.20)	4.15 (1.42)	0.61	—	
Systemic vascular resistance (dynes · sec/cm^5)	1.32 (1.93)	1.24 (2.60)	1.37 (0.98)	0.26	—	
Respiratory						
Respiratory rate (breaths/min)	13.5 (2.5)	15.3 (3.1)	15.9 (2.5)	4.35	.02	P < C
Tidal volume (mL)	445 (123)	383 (63)	317 (70)	11.21	.0001	P > C
Tidal volume, sighs removed (mL)	369 (109)	343 (51)	291 (74)	4.77	.02	P > C
Minute volume (L/min)	5.98 (0.92)	5.86 (1.29)	5.07 (0.87)	2.62	(.08)	
Duty cycle (ratio)	0.297 (0.037)	0.338 (0.062)	0.331 (0.032)	4.39	.02	P < G = C
Inspiratory flow rate (mL/sec)	301 (49)	279 (58)	241 (40)	8.50	.0007	P > C
End-tidal pCO_2 (mm Hg)	33.8 (6.9)	38.2 (5.0)	39.5 (3.4)	5.22	.01	P < C
Sighs > 2 · normal (number/min)	0.734 (0.384)	0.474 (0.321)	0.378 (0.264)	5.25	.009	P > C
Apneas > 5 sec (number/min)	0.332 (0.443)	0.226 (0.291)	0.103 (0.258)	1.98	—	

PD, panic disorder; GAD, generalized anxiety disorder; SC, skin conductance.
[a] df = 2,47; df = 2,42 for SC level and 2,40 for end-tidal pCO_2 due to device malfunctions.

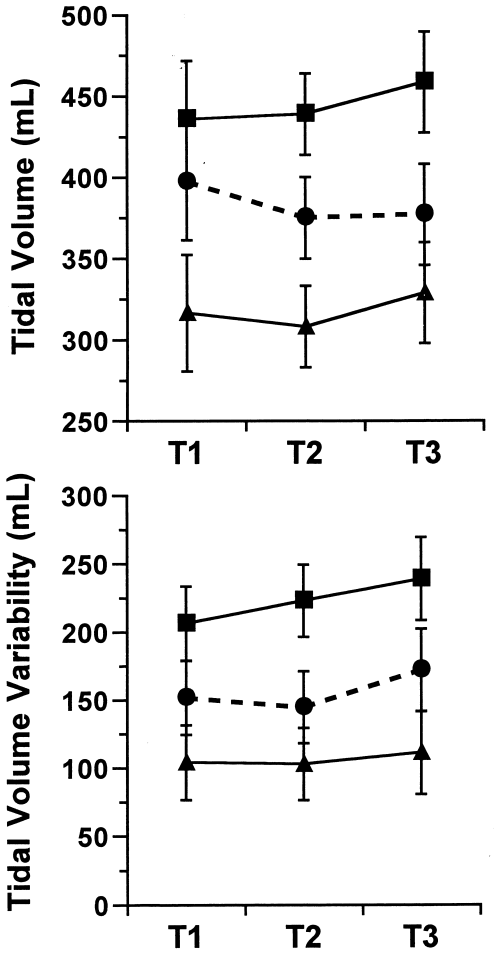

Figure 1. Means and SEs of tidal volume and tidal volume variability for panic disorder patients (■), generalized anxiety disorder patients (●), and control subjects (▲) over three consecutive 10-min epochs of the 30-min quiet sitting period.

Tidal volume variability also distinguished groups when calculated by methods other than complex demodulation. Like with complex demodulation, group means from rMSSDs were characterized by the inequality P > G > C. Means ± SDs in milliliters for the three groups, respectively, were 279 ± 128, 187 ± 39, and 125 ± 75 [$F(2,47) = 12.63$, $p < .0002$]. Coefficient of variation was somewhat less discriminatory [$F(2,47) = 4.96$, $p < .01$, P > C].

To allow us to compare these heart rate and skin conductance results to previous ones (Roth et al 1998a), we examined complex demodulated amplitudes in three previously used narrower frequency bands: 0.004–0.025 Hz (ultralow), 0.025–0.07 Hz (low), and 0.07–0.14 Hz (middle). All Group effects and Group × Time interactions, had ps > .2. Tidal volume, however, showed significant Group effects in all three bands [Fs(2,47) > 9.04, ps < .0005], whether or not sighs were included. The same was true for pCO_2 [Fs(2,40) > 4.07, ps < .03]. For respiratory rate, only the middle band group effect was significant [$F(2,47) = 3.76$, $p < .03$]. No Group × Time interactions were significant for any of these respiratory measures in any band.

Influence of State Anxiety

That differences between GAD and PD groups were related to differences in state anxiety is unlikely because mean levels for several state anxiety measures did not differ between them. To further assess the influence of state anxiety, we performed analyses of covariance (ANCOVAs) on GAD and PD patients on the measures in Tables 3 and 4, selecting as the covariate each subject's mean of SUD anxiety prior to and following sitting. This covariate had the best face validity as an estimate of anxiety during the sitting period, although in fact all three SUD anxiety measures were highly intercorrelated. (Across groups, the rs were in the range (.79–.90) and within the PD group in the range (.70–.91), within GAD (.71–.82), and within control subjects (.65–.69).) The ANCOVAs yielded three significant differences. Sigh frequency was significantly greater in PD than GAD [$F(1,28) = 4.86$, $p < .03$], although the Tukey means test had failed to fall below the $p = .05$ level. Significant means tests differences for duty cycle [$F(1,28) = 5.28$, $p < .03$] and tidal volume variability [$F(1,28) = 4.53$, $p < .04$] were confirmed by ANCOVAs. One reason that ANCOVAs did not change results much was that this estimate of anxiety during sitting did not correlate significantly with these measures with either the PD or GAD groups with the exception of mean HR, which in the GAD group had an $r(14) = .60$ ($p < .03$).

Panickers versus Nonpanickers

Although the numbers of subjects are small, among the PD patients the six panickers (two of who were of the respiratory subtype) were compared statistically to the ten nonpanickers. They did not differ on any of the variables in Table 1. For the self-report measures listed in Table 2, panickers had higher scores (t test ps < .03 to .0001) than nonpanickers on all the Symptom Questionnaire measures except "tingling or numbness," but not on the SUD anxiety measures. For the variables listed in Table 3, only one differed. The duty cycle ratio was smaller ($p < .02$) in panickers (.273 ± .036) than nonpanickers (.315 ± .031). None of the variability variables listed in Table 4 distinguished panickers and nonpanickers.

To assess the extent to which the results depended on patients reporting panic attacks while sitting, the six PD patients and the one GAD patient who panicked were excluded, and the results recalculated. For Table 1 and the

Table 4. Physiologic Measures: Variability (SD) by Complex Demodulation (Frequency Range 0.004–0.14 Hz) during 30 Min of Quiet Sitting

	PD	GAD	Control subjects	F^a	p	Post hoc
Electrodermal and cardiovascular						
SC level (μSiemens)	0.97 (0.68)	0.80 (0.81)	0.67 (1.05)	0.46	—	
Heart rate (beats/min)	3.32 (1.95)	4.33 (2.66)	3.24 (1.63)	1.68	—	
Systolic blood pressure (mm Hg)	8.23 (4.51)	9.27 (6.39)	8.11 (3.38)	0.33	—	
Diastolic blood pressure (mm Hg)	4.59 (1.78)	6.58 (4.55)	4.98 (1.98)	2.57	(.09)	
Stroke volume (mL)	3.90 (1.56)	6.13 (4.02)	4.47 (2.57)	3.11	(.06)	
Cardiac output (L/min)	0.24 (0.10)	0.38 (0.22)	0.29 (0.20)	2.83	(.07)	
Systemic vascular resistance (dynes · sec/cm^5/1000)	3.46 (5.40)	3.04 (5.82)	3.29 (3.61)	0.03	—	
Respiratory						
Respiratory rate (breaths/min)	3.36 (1.19)	3.59 (1.31)	2.53 (1.59)	3.24	.05	P = G > C
Tidal volume (mL)	222 (112)	156 (73)	106 (60)	9.99	.0002	P > G > C
Tidal volume, sighs removed (mL)	105 (49)	100 (41)	64 (29)	6.17	.005	P = G > C
Minute volume (L/min)	2.09 (0.88)	1.94 (0.89)	1.31 (0.64)	5.47	.007	P > C
Duty cycle (ratio)	0.070 (0.028)	0.079 (0.031)	0.049 (0.027)	5.90	.005	P = G > C
Inspiratory flow rate (mL/sec)	98.6 (46.8)	85.9 (43.7)	57.7 (31.1)	5.42	.008	P > C
End-tidal pCO_2 (mm Hg)	2.01 (1.46)	1.35 (0.54)	1.03 (0.33)	4.90	.01	P > C

PD, panic disorder; GAD, generalized anxiety disorder; SC, skin conductance.
[a]df = 2,47; df = 2,42 for SC level and 2,40 for end-tidal pCO_2 due to device malfunctions.

anxiety measures in Table 2, all previously significant results continued to be so, and post hoc tests of means documented exactly the same inequalities. Of the other measures in Table 2, only shortness of breath and heart racing remained significant in both cases with the inequalities P = G > C. For Table 3, two measures, respiratory rate and duty cycle, lost their significance whereas the others did not, maintaining the same inequalities except for end-tidal pCO_2 for which they became more specific for PD, namely P < G = C. For variability measures in Table 4, changes occurred only in respiratory rate and end-tidal pCO_2, which lost their significance, and in the inequalities for tidal volumes with sighs removed, which became P > C. Thus, observed group differences depended only in a few details on a specific contribution from the minority of patients reporting panic.

Restriction to Diagnostically Nonoverlapping Groups

Inclusion criteria for the analyses here were based on two assumptions about how diagnosis determines physiologic characteristics. Current but not past diagnoses are relevant (three GAD patients had a history of PD), and a diagnosis of PD takes precedence over one of GAD (three PD patients met criteria for current GAD). To determine how much these assumptions influenced the results, all of the analyses listed in Tables 2, 3, and 4 were redone following excluding the GAD patients with a history of PD and the PD patients with current GAD. We found that the patterns of significance between groups listed in the post hoc columns were identical following removing these six patients, except in the case of variability of inspiratory flow rate, whose pattern changed from P > C to P = G > C.

Discussion

Our hypothesis that PD patients would be less stable physiologically than control subjects was confirmed for tidal volume and a number of other respiratory measures: respiratory rate, minute ventilation, duty cycle, inspiratory flow rate, and end-tidal pCO_2. These findings are probably interrelated causally: instability of respiratory drive and timing, for example, could produce instability in end-tidal pCO_2 via changes in ventilation; or, vice versa, fluctuations in pCO_2 could stimulate instability in respiratory drive and timing via chemical feedback loops (Modarreszadeh and Bruce 1994). Large breaths (sighs) are undoubtedly a major contributor to this instability because the number of sighs is significantly greater in PD patients than control subjects; however, sighs as we defined them do not account for all the group differences because several analyses where sighs were excluded continued to show respiratory differences between PD patients and control subjects.

Respiratory instability in PD patients was accompanied by a relative hypocapnia persisting throughout the 30-min period. Hypocapnia has been observed at rest in PD in a number of studies (Hegel and Ferguson 1997; Papp et al 1997; Rapee 1986), and is consistent with larger mean tidal volumes in the PD patients, but because in our study their respiratory rates were lower, their minute ventilations

did not turn out to be significantly higher. We recently observed prolonged hypocapnia without increased minute ventilation in PD patients compared to social phobia patients and control subjects during recovery from voluntary hyperventilation (Wilhelm et al, in press). Possible explanations include a decreased production rate of CO_2 or a shift to anaerobic metabolism. In addition, tidal volume irregularity in itself might lower pCO_2 more than predicted by minute ventilation. If the relationship between tidal volume and pCO_2 lowering is not linear, combinations of deep and shallow breaths might result in different pCO_2 levels from those produced by breaths consistently near a mean tidal volume. Observed negative correlations between tidal volume variability and pCO_2 level support such a mechanism.

To what extent our results represent a "state" effect induced by the experimental context and to what extent they represent persisting "trait" characteristics of these patients can only be guessed in the absence of more prolonged recordings in a variety of settings. The quiet sitting procedure like all supposed baselines was undoubtedly influenced by what went on before it, the conditions during it, and what the subject anticipates will happen after it. Ten minutes before patients had held their breath for 30-sec periods, and pCO_2 levels of PD patients had become significantly lower than those of control subjects during the procedure. One interpretation of our current findings is that suffocation fears were stimulated in PD patients during breath holdings (Klein 1992) and that compensatory hyperventilation accomplished by intermittent deep breaths followed breath holdings, persisting for the next 40 min. Against this interpretation is that breath holdings did not provoke more SUD anxiety in PD patients than in GAD patients or control subjects, and at the end of the procedure had not changed anxiety levels in any of the groups from the before-breath-holding levels. Also against it is the undiminished persistence of the respiratory effects for 40 min (for tidal volumes, see Figure 1). In any case, a replication of our results should be undertaken with and without prior breath holding. Confirmation of such long-lasting breath holding effects is unlikely but would be of extraordinary interest.

Conditions during testing is a second factor that influences results. It should not be assumed that sitting for 30 min is a neutral experience for any of the subjects. In some people, prolonged sitting provokes impatience, restlessness, and a feeling of confinement. For PD patients, an additional threat may have been the opportunity to perceive and misinterpret somatic sensations, because competition from environmental cues is reduced (see Pennebaker 2000 for a review of how such a reduction increases illness symptoms in other contexts). Promoting relaxation in quiet settings can even precipitate panic attacks in PD patients (Adler et al 1987; Cohen et al 1985). Indeed, six of our PD patients reported attacks along with one of the GAD patients. Yet most of our group differences were independent of panic attacks. The third factor, anticipation of what will happen afterward, was less operative here, because quiet sitting was the last event of the session.

The most direct interpretation of our results is that they indicate diagnostic specificity (which is tantamount to a specificity of kind of anxiety, i.e., panic vs. worry or anticipatory anxiety). In favor of specificity is the fact that despite comparable self-reported anxiety in the two anxious groups, PD patients were more physiologically different from control subjects than GAD patients, although in ANOVAs the difference between PD and GAD was only significant for duty cycle and tidal volume instability. ANCOVAs controlling for self-reported anxiety confirmed the results for duty cycle and tidal volume instability, and found significantly more sighs in PD than in GAD. For other physiologic measures, such as end-tidal pCO_2, the values of GAD patients were intermediate between PD patients and control subjects but not significantly different from either, perhaps because of Type II errors related to the small number of subjects and the use of the conservative Tukey test for post hoc comparisons. (In addition, GAD patients had not quite significantly larger stroke volume and other cardiovascular system fluctuations than other groups.) An alternative interpretation, however, is that the differences between PD and GAD patients represent a quantitative anxiety intensity effect rather than a qualitative diagnostic effect. PD patients may actually have been more anxious than GAD patients, but because of a reporting bias rated themselves less anxious than they actually were. Panic disorder patients, having experienced more intense anxiety than GAD patients, may have a differently anchored internal SUD scale.

As explained in the Introduction, a motivation for this study was to look for unprovoked fluctuations in biological features known to be associated with full-blown attacks. Cardiovascular, respiratory, and electrodermal variables sensitive to anxiety seemed like good candidates but, surprisingly, only respiratory variables showed group differences. Fluctuations in cardiac output and other hemodynamic variables, as one might expect with intermittent sympathetic discharge, did not distinguish the groups. This is contrary to our own recent findings of greater heart rate and skin conductance instability in PD patients during a quiet sitting period (Roth et al 1998a). In that study, instability was largely confined to PD patients who reported panic, and whose small number in the current study afforded little statistical power. In addition, in the previous study, the quiet sitting period immediately followed a

highly activating speaking task, the physiologic effects of which persisted throughout the 10 min of sitting.

A possible explanation for the predominance of respiratory findings is that respiratory variables are the most sensitive indicators of anxiety, and that the fluctuations in anxiety were so small that only the most sensitive variables registered them. However, to equate individual respiratory fluctuations with clinical or subclinical panic attacks is dubious. Panickers among the PD patients were not greater than nonpanickers on any of our respiratory variability measures. Perhaps certain respiratory events enable attacks, but these events are distinct from the psychological and physiologic changes that accompany attacks themselves and are not synchronized with individual attacks. Having patients report their state of anxiety or panic and of dyspnea at short intervals might help decide this matter at least for attacks greater than the threshold of awareness, though frequent reporting adds its own psychological and physiologic perturbations. In any case, whatever the exact relationship between respiration and specific clinical symptoms, our findings add to others in underlining the importance of respiratory physiology for the understanding of panic disorder.

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