Characteristics of Sighing in Panic Disorder

Frank H. Wilhelm, Werner Trabert, and Walton T. Roth

Background: *Sighs, breaths with larger tidal volumes than surrounding breaths, have been reported as being more frequent in patients with anxiety disorders.*

Methods: *Sixteen patients with panic disorder, 15 with generalized anxiety disorder, and 19 normal control subjects were asked to sit quietly for 30 min. Respiratory volumes and timing were recorded with inductive plethysmography and expired pCO_2, from nasal prongs.*

Results: *Panic disorder patients sighed more and had tonically lower end-tidal pCO_2s than control subjects, whereas generalized anxiety disorder patients were intermediate. Sighs defined as >2.0 times the subject mean discriminated groups best. Sigh frequency was more predictive of individual pCO_2 levels than was minute volume. Ensemble averaging of respiratory variables for sequences of breaths surrounding sighs showed no evidence that sighs were triggered by increased pCO_2 or reduced tidal volume in any group. Sigh breaths were larger in panic disorder patients than in control subjects. After sighs, pCO_2 and tidal volume did not return to baseline levels as quickly in panic disorder patients as in control subjects.*

Conclusions: *Hypocapnia in panic disorder patients is related to sigh frequency. In none of the groups was sighing a homeostatic response. Panic disorder patients show less peripheral chemoreflex gain than control subjects, which would maintain low pCO_2 levels after sighing.*
Biol Psychiatry 2001;49:606–614 © *2001 Society of Biological Psychiatry*

Key Words: Anxiety disorders, respiration, end-tidal pCO_2, chemoreceptors, control of breathing, pulmonary ventilation

Introduction

Sighing respiration is a fundamental vertebrate behavior: even isolated vertebrate brain stem networks produce sighlike discharges (Lieske et al 2000). In the initial analysis of an experiment comparing quietly sitting panic disorder (PD) and generalized anxiety disorder (GAD) patients with control subjects, we reported more respiratory instability and sighing in PD patients (Wilhelm et al 2001). Either of two prominent theories of PD, the suffocation false alarm (Klein 1992) and hyperventilation (Ley 1990) theories, might have predicted more deep breaths or sighs. An individual with an overly sensitive suffocation alarm might be inclined to take periodic deeper breaths to test the air supply. Furthermore, such breaths might lower the pCO_2 safely below the threshold of the CO_2 chemoreceptor, whose firing is one source for a feeling of suffocation. In contrast, hyperventilation theories ascribe panic to the lowered pCO_2 itself, which deeper breaths could cause.

Increased sighing in an anxiety disorder is unlikely to be a chance finding, since it has been observed several times previously. In early spirograms of psychiatric patients, "psychoneurotic" patients were observed to sigh frequently (Finesinger 1943). The frequency of sighs distinguished chronically anxious patients from patients with various lung diseases (Tobin et al 1983). Lactate infusions, which trigger panic attacks in PD patients (Liebowitz et al 1984), increased sighing in PD patients and patients with late–luteal phase dysphoric disorder (Schwartz et al 1996). Sighing was more frequent in PD patients than in social phobia patients or control subjects during recovery from voluntary hyperventilation (Wilhelm et al, in press). Abelson et al (2001) found PD patients to show more respiratory irregularity, with more sighs than control subjects under several experimental conditions.

This article reports an in-depth analysis of sigh breaths and of the sequence of breaths immediately preceding and following them, from the data set described in our initial report (Wilhelm et al 2001). Respiratory volumes were measured from external belts, and end-tidal pCO_2 measurements from nasal prongs, which are less intrusive or threatening than using a mouthpiece or closed system. First, we set out to characterize the distribution of volumes of individual breaths, their sequential dependencies, the temporal distribution of high volume breaths (sighs), and the volume criterion for a sigh that best distinguished our groups from each other. Second, by examining the sequence of breaths around sighs we tested hypotheses about the events triggering sighs and about the homeostatic feedback mechanisms that keep pCO_2 constant. Specifi-

From the Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, and the Department of Veterans Affairs Health Care System, Palo Alto, California. WT is currently affiliated with the Sanitas Klinik Garmisch, Garmisch-Partenkirchen, Germany.

Address reprint requests to Frank H. Wilhelm, Ph.D., Stanford University, VAPAHCS (116F-PAD), 3801 Miranda Avenue, Palo Alto CA 94304.

Received March 3, 2000; revised July 18, 2000; accepted July 24, 2000.

0006-3223/01/$20.00
PII S0006-3223(00)01014-3

cally, we hypothesized that in PD patients sigh breaths would be preceded by breaths with lower tidal volume (TV), lower instantaneous minute volume (MV), and higher pCO_2 than nonsigh breaths, since this kind of breath would tend to trigger their sensitive suffocation alarm and trigger a compensatory deeper breath. Furthermore, we hypothesized that PD patients would show evidence of higher chemoreceptor gain, which has been observed when these patients were exposed to increasing pCO_2 concentrations (Lousberg et al 1988; Pain et al 1988). After sighs, which lower pCO_2, higher gain would be manifested by faster recovery of pCO_2 to presigh levels (Khoo and Marmarelis 1989).

Methods and Materials

Subjects

Sixteen patients with PD, 15 with GAD, and 19 psychiatrically healthy control subjects were recruited and diagnosed as described previously (Wilhelm et al 2001). 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. All patients and normal control subjects denied taking psychoactive or cardiovascularly active medication in the two weeks before testing. None of the subjects reported current epileptic, respiratory, or cardiovascular disease. Mean (SD) ages were 44.0 (9.0) for PD, 37.3 (9.0) for GAD, and 43.7 (16.1) for control subjects. Percentages of women were 69% for PD, 60% for GAD, and 63% for control subjects. Further psychologic test information and other details about these subjects can be found in Wilhelm et al (2001).

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 mouths sealed and breathe only through their noses so that the nasal prongs could sample the air they breathed in and out. In addition, they were to keep their eyes open. Ten minutes before beginning this quiet sitting period, subjects had completed a procedure where they had held their breaths for 30 sec 12 times at 60-sec intervals (Roth et al 1998). Although the mean Subjective Units of Distress (SUD) 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 for control subjects.

Self-Report Measures

Details on self-report measures are given in Wilhelm et al (2001). In brief, on an anxiety SUD scale ranging from 0 (not at all) to 10 (extremely strong), PD patients and GAD patients gave themselves mean self-ratings between 4.0 and 5.0 both before and after the sitting period, whereas control subjects had means around 0. Panic disorder and GAD patients did not differ statistically from each other, but both were more anxious than control subjects. Six PD patients, one GAD patient, but no control subject met our self-report criteria (similar to those used by Sanderson et al 1989) for panic attacks during the sitting period.

Physiologic Measures

Recordings were made of several physiologic channels. The methodology of recording the various channels (skin conductance [SC], heart rate [HR], abdominal and thoracic respiration, and expiratory pCO_2) and reducing the data from them are described in Wilhelm et al (2001).

Statistical Analysis

We quantified the sequential statistical dependencies of TVs using the autocorrelation procedure described by Tobin et al (1995), in which each individual sequence of TVs was correlated with an exact copy of itself iteratively, with the copy being shifted one breath lag at a time in relation to the original. To increase the stability of estimates the TV series was detrended using higher order (up to order 5) polynomials and then truncated ("clamped") at 2 SDs above and below the mean (i.e., values exceeding this threshold were replaced by the threshold value).

To look for respiratory precursors and sequelae of sigh breaths, ensemble averages were calculated for each subject for each sigh breath (t0) and for three breaths preceding ($t - 3$, $t - 2$, $t - 1$) and following it ($t + 1$, $t + 2$, $t + 3$) and for each nonsigh breath and the three breaths preceding and following it. Thus, the resulting seven-breath sequences were centered on sigh or nonsigh breaths, respectively. Sequences did not exclude breaths of the other category in positions other than the synchronizing one, and did not exclude the same breath being in multiple ensembles, since each successive breath became the synchronizing breath for a new ensemble. This kind of ensemble averaging makes the fewest assumptions about causal links between sigh and nonsigh breaths. In addition, to look for a possible heterogeneity in type of sigh, we calculated within-subject variability (as SD) of change in pCO_2 from the $t - 3$ to $t - 1$ breath and from the $t + 1$ to the $t + 3$ breath, and entered the SDs into an analysis of variance (ANOVA) with the factors Group and Time.

For SC and HR, a continuous time period of 12 sec before and 16 sec after the onsets of sigh and of nonsigh inhalations were subjected to ensemble averaging. The seven positions that correspond to the breath-by-breath analyses were consecutive 4-sec means for each subject, 4 sec approximating the average length of a single breath cycle. However, these were not adjusted for individual differences in respiratory rate (RR) because activation in SC and HR was expected to follow a clock-time rather than a breath-time base.

Ensemble averages were analyzed using repeated-measures ANOVAs. The overall ANOVAs included the factors Group (PD patients, GAD patients, control subjects), Sigh (sigh and nonsigh

Table 1. Normal Distribution and Sigh Parameters: Means (SDs)

	PD	GAD	Control Subjects	$F(2,47)$	p	Post hoc
Tidal volume						
Mean (mL)	445 (123)	383 (63)	317 (70)	11.21	.0001	PD > control subjects
SD (mL)	239 (88)	177 (66)	123 (51)	12.13	.0001	PD > GAD = control subjects
Skew	3.10 (1.30)	2.99 (1.91)	4.04 (1.60)	2.26	ns	
Kurtosis	16.8 (10.2)	21.6 (20.1)	31.3 (19.0)	3.26	.05	PD < control subjects
Respiratory rate						
Mean (breaths/min)	13.5 (2.5)	15.3 (3.1)	15.9 (2.4)	4.35	.02	PD < control subjects
SD (breaths/min)	4.38 (1.34)	4.36 (1.71)	2.70 (1.27)	7.96	.001	PD = GAD > control subjects
Skew	1.52 (1.05)	1.44 (1.99)	−0.20 (1.10)	8.36	.0008	PD = GAD > control subjects
Kurtosis	12.6 (10.7)	17.1 (28.7)	8.5 (3.4)	1.10	ns	
Sighs						
Number/min	.70 (.38)	0.47 (.32)	.36 (.26)	4.97	.02	PD > control subjects
Run length	1.13 (0.16)	1.17 (0.20)	1.15 (0.19)	0.19	ns	

Significant differences represented by inequalities are transitive: for example, if A = B > C, then A > C. PD, panic disorder; GAD, generalized anxiety disorder.

breath-containing ensembles), and Position in the ensemble (t − 3 to t + 3, with t0 being the synchronizing sigh or nonsigh response). p levels were corrected for nonsphericity using the Greenhouse–Geisser ϵ. When overall ANOVAs were significant, follow-up ANOVAs and Tukey means tests ($p < .05$) with comparison-specific error terms for effects involving the Group and Time factors were calculated. Group main effects and Group × Time interactions were the focus of our analysis.

The statistical analyses can be classified into those that test *a priori* hypotheses and those that are exploratory and that because of their number are particularly prone to Type I errors. Our principal hypotheses were that PD patients would show more CO_2 chemoreceptor sensitivity than other groups, as manifested by a greater decrease in TVs in the three breaths following the sigh response (Khoo and Marmarelis 1989), and that their sigh responses would be preceded by breaths with lower TVs and increased end-tidal pCO_2s. We expected that sighs in PD would be preceded by sympathetic discharge, a kind of fear response, indicated by increased electrodermal activity. The main respiratory variables under scrutiny were end-tidal pCO_2, TV, and RR. Minute volume, duty cycle (DC), and inspiratory flow rate (IFR) are dependent on the main variables computationally and statistically, and were analyzed for heuristic reasons. Exploratory analyses tested cardiovascular measures, examined the distribution of TVs and RRs, the run length of sighs, and determined what definition of sighs best separated our groups.

Results

Distributions

Normal distribution parameters of TV and RR over the entire 30 min were calculated for individual subjects. As presented in Table 1, SDs of TVs are larger in PD patients than in the other groups, and the PD patients have a flatter distribution (less kurtosis) than control subjects. The distribution of TVs in all groups is positively skewed, but skewness does not differ significantly between groups, although this might be expected from the greater number of sighs in PD. As Figure 1 illustrates, TVs in the upper L range tend to be more frequent in the PD patients. (t tests indicate a significant difference between PD patients and GAD patients or control subjects in the range 0.8–1.4 L.) More TVs in this range represent a greater percentage of sighlike breaths, since sighs by the employed criteria would fall in this range. Whether distributions tailed off

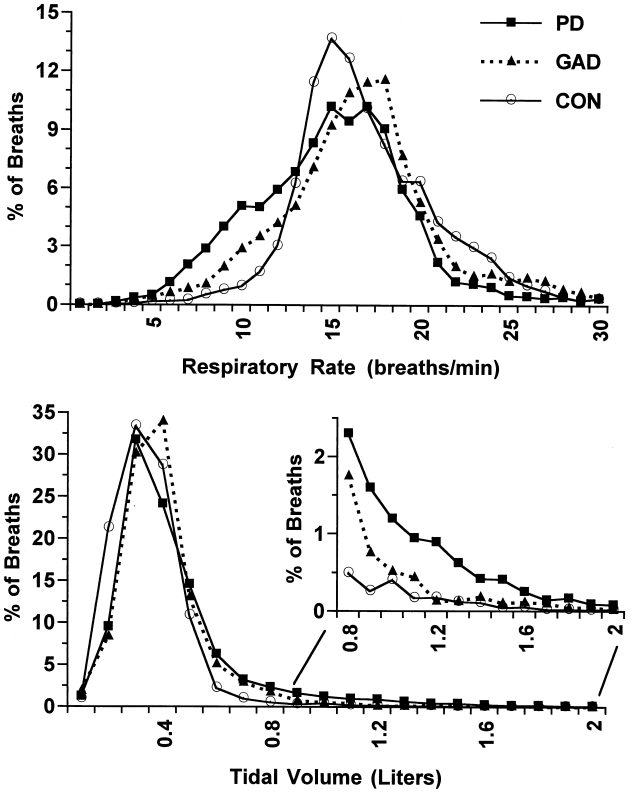

Figure 1. Distribution of tidal volumes and respiratory rates for the three groups. The inset plots the 0.8- to 2.0-L part of the tidal volume curve at a higher percentage resolution. PD, panic disorder; GAD, generalized anxiety disorder; CON, control subjects.

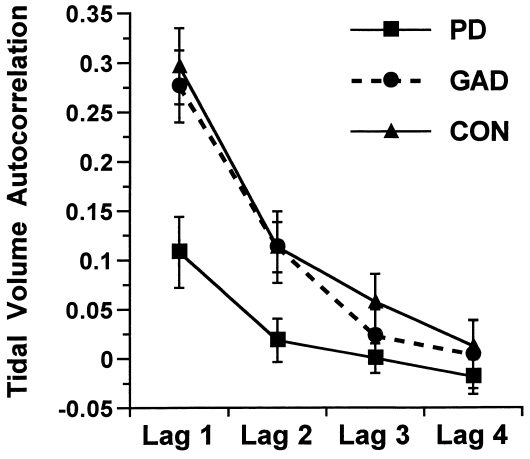

Figure 2. Autocorrelations of consecutive tidal volumes, and their standard errors, at lags 1, 2, 3, and 4 for the three groups. PD, panic disorder; GAD, generalized anxiety disorder; CON, control subjects.

monotonically or whether a second positive mode existed for deep breaths was equivocal after inspecting individual distributions.

Panic disorder and GAD patients have higher SDs of intervals between breaths (expressed as RR) than control subjects. The distribution of these intervals is significantly skewed towards longer intervals between breaths in patients. Figure 1 shows that rates of 7–12 breaths/min corresponding to intervals of 5.0–8.6 sec tend to be more frequent in PD patients than in control subjects, whereas rates of 20–24 corresponding to intervals of 2.5–3.0 sec tend to be less frequent.

Sequential Dependencies of Tidal Volumes

Figure 2 presents autocorrelations of successive tidal volumes at four lags. Kruskal-Wallis ANOVA by ranks showed group differences at lags 1 [$H(2,50) = 11.73$, $p < .003$] and 2 [$H(2,50) = 6.71$, $p < .04$], but not lags 3 or 4. Post hoc Mann-Whitney U tests ($p < .05$) showed the pattern PD < GAD = control subjects for both lag 1 and lag 2. Since lower correlations at multiple lags could be wholly due to single, infrequent large breaths, an analysis substituting for those tidal volumes the individual's average was performed. Group differences were again present for lags 1 [$H(2,50) = 11.49$, $p < .004$] and 2 [$H(2,50) = 9.70$, $p < .008$], with PD < GAD = control subjects.

Another way of quantifying stability in autocorrelations is to evaluate short-term respiratory "memory," the number of consecutive breath lags displaying autocorrelation coefficients statistically significantly different from 0 at the $p < 0.01$ level (r is adjusted for the number of breaths recorded for each individual). Shorter memory indicates more randomness of respiratory regulation as indexed by these statistical dependencies (Tobin et al 1995). These TV memories are 0.56 ± 0.89 lags for PD patients, 1.80 ± 2.62 for GAD patients, and 2.42 ± 3.83 for control subjects. There is a group difference [$H(2,50) = 8.75$, $p < .02$] with a pattern of significance using Mann-Whitney U tests of PD < GAD = control subjects. When sighs are replaced by the individual's average values, these memories are 0.75 ± 0.77 lags for PD patients, 2.13 ± 2.56 for GAD patients, and 2.79 ± 3.72 for control subjects. There is a group difference [$H(2,50) = 11.04$, $p < .005$] with the same pattern of significance using Mann-Whitney U tests of PD < GAD = control subjects.

Sighs

Sigh frequency, defined as >2.0 times the mean TV, distinguished PD patients from control subjects, whereas GAD patients did not significantly differ from either PD patients or control subjects. The mean run length was slightly above 1 in each group. On average, 88% of the runs were comprised of a single sigh, 9% of two, and 2% of three; proportions did not differ significantly between groups (p's > .3). In post hoc discriminant analyses we examined the ability of factors between 1.1 and 5.0 times individual means, incremented in steps of 0.1, to give a definition that would best distinguish the groups. In fact, for our sample, the initial value of 2.0 was the best [$F(2,47) = 5.49$, $p < .008$]. Although it classified 56% of PD patients and 84% of control subjects correctly, it did not classify any of the GAD patients correctly: 80% were classified as control subjects and 20% as PD patients. The best criteria for distinguishing pairs of groups were 1.9 for PD (56% correct) versus control subjects (84% correct), 2.4 for PD (62% correct) versus GAD (67% correct), and 1.5 for GAD (33% correct) versus control subjects (74% correct).

Our test of possible heterogeneity in type of sigh, which compared within-subject SDs of change in pCO_2 before and after sighs, did not find a significant Group × Time interaction ($p = .11$).

Ensemble Averages: Respiratory Effects

As illustrated in Figures 3 and 4, respiratory measures are quite constant in the nonsigh ensembles except in the middle position, where the nonsigh breaths selected to form the ensemble are averaged. This breath deviates slightly from the others for several measures because sighs are allowed to occur and occasionally do occur in all the positions except this one. Sigh ensembles, on the other hand, show a marked effect of the sigh in the middle position, and certain other pre- and postsigh effects. Analyses of variance that included all three groups, sigh

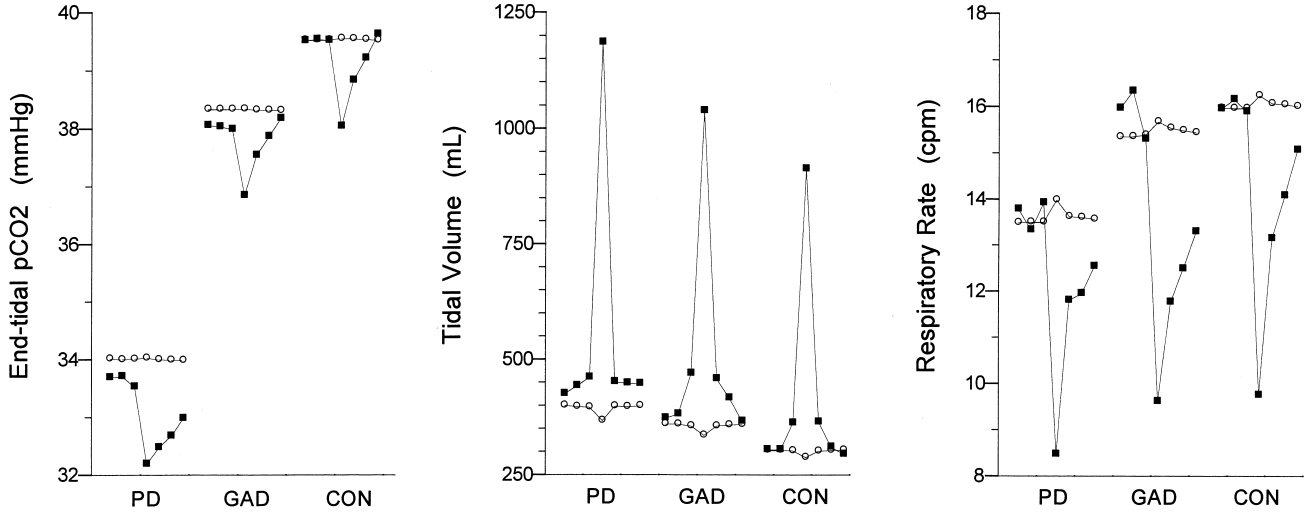

Figure 3. Sigh (■) and nonsigh (○) ensemble averages of pCO_2, tidal volume, and respiratory rate for the three groups. Averages are of the three breaths preceding a sigh, the sigh, and the three breaths following the sigh. PD, panic disorder; GAD, generalized anxiety disorder; CON, control subjects; cpm, cycles per minute.

and nonsigh breath-containing ensembles, and all seven ordinal positions of the ensembles showed significant three-way interactions for pCO_2 [$F(12,240) = 2.59$, $p < .003$], TV [$F(12,282) = 2.85$, $p < .001$], and RR [$F(112,282) = 2.07$, $p < .02$]. Three important respiratory variables computationally related to the first three (illustrated in Figure 3) did not show significant three-way interactions, but exhibited significant main group effects: MV [$F(2,47) = 3.31$, $p < .05$], DC [$F(2,47) = 3.39$, $p < .05$], and IFR [$F(2,47) = 6.93$, $p < .003$]. The statistical significance of these more global ANOVAs justified specific follow-up ANOVAs and comparisons of means that follow.

Nonsigh ensembles were tested for background effects not associated with sighing. As would be expected, since none of the positions in the sequence represented different conditions, only Group effects were observed, and these occurred for all respiratory variables except MV. No significant effects were found for autonomic variables. As documented in Table 2, PD patients had greater IFR, an indication of greater air hunger. Their lower pCO_2s were not readily explained, since their greater TVs were offset

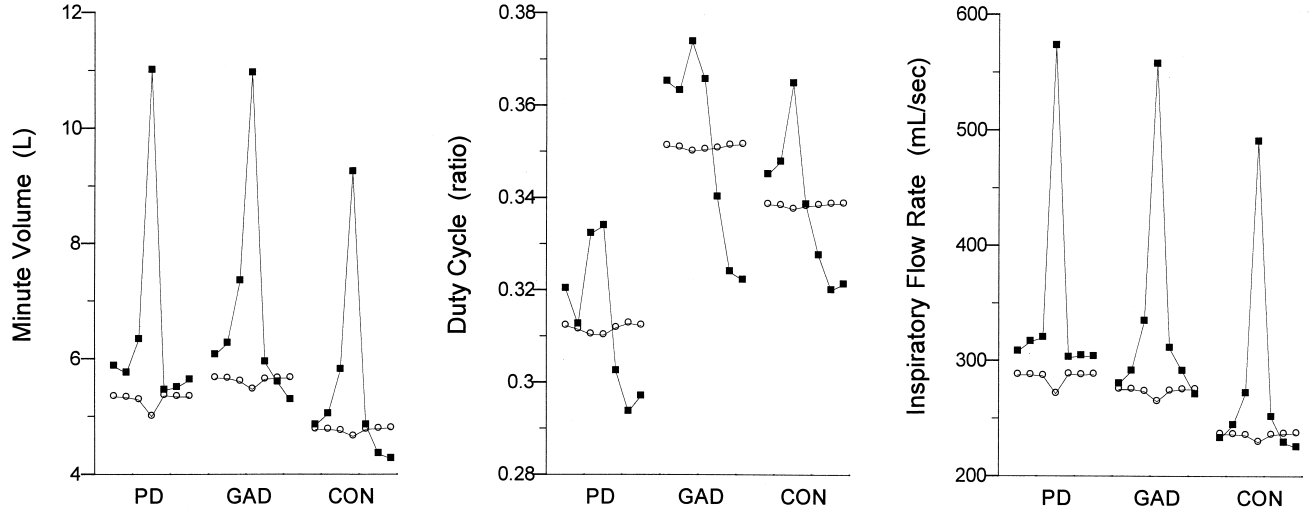

Figure 4. Sigh (■) and nonsigh (○) ensemble averages of minute volume, duty cycle, and inspiratory flow rate for the three groups. Averages are of the three breaths preceding a sigh, the sigh, and the three breaths following the sigh. PD, panic disorder; GAD, generalized anxiety disorder; CON, control subjects.

Table 2. Results of Analyses of Variance for Mean Comparison of Groups in Nonsigh Ensembles

	$F(2,47)^a$	p	Post hoc
pCO_2	4.82	.02	PD < control subjects
TV	7.10	.002	PD > control subjects
RR	3.95	.03	PD < control subjects
MV	3.03	ns	
DC	4.24	.02	PD < GAD = control subjects
IFR	6.17	.005	PD > control subjects

PD, panic disorder; TV, tidal volume; RR, respiratory rate; MV, minute volume; DC, duty cycle; GAD, generalized anxiety disorder; IFR, inspiratory flow rate.

[a]Degrees of freedom are 2,40 for pCO_2.

by longer RRs resulting in MVs that are not significantly greater than the other groups. Thus, much of the source of the sustained hypocapnia is likely to reside in the sigh ensembles.

Sigh ensembles were analyzed in terms of sighs, presigh sequences, and postsigh sequences using the nonsigh ensembles as reference by including the Sigh/nonsigh factor. *Sighs* showed a significant Group × Sigh/nonsigh interaction effect only for TV [$F(22,47) = 5.25$, $p < .009$]. Post hoc means tests showed the pattern PD > GAD = control subjects. Tidal volumes, already selected to be >2.0 times the average for the individual, turned out to be larger in PD, perhaps a consequence of the larger TVs in nonsigh sequences setting a higher criterion. In spite of the larger TVs, the drop in pCO_2 associated with the sigh breath did not differ between groups [$F(2,40) = 0.55$, ns]. Of course, the exhalation after the sigh inspiration was associated with a highly significant drop in pCO_2 in all groups [$F(1,40) = 115.12$, $p < .00001$].

Analyses of variance of *three trials preceding the sigh trial* with the factors Group, Sigh/nonsigh, and Position (1, 2, 3), were devoid of significant interactions involving Group. However, several Sigh/nonsigh × Position effects confirmed that breaths preceding sighs were different. We had assumed that sigh breaths would be preceded by relatively higher pCO_2 and smaller TV. However, pCO_2 showed no effects and TV, a two-way interaction [$F(2,94) = 17.4$, $p < .0001$] that, according to post hoc tests, resulted from a larger TV for the t − 1 breath than in the corresponding position of the nonsigh ensemble. Follow-up analyses of two-way interactions for MV [$F(2,94) = 16.2$, $p < .0001$], DC [$F(2,94) = 4.29$, $p < .02$], and IFR [$F(2,94) = 10.4$, $p < .0001$] showed that the t − 1 breath also had a higher MV, DC, and IFR than the corresponding breath of the nonsigh ensemble. For each of the four significant variables, the t − 1 breath had higher values than the t − 2 breath, which did not differ from the t − 3 breath.

Analyses of variance of *three trials following the sigh trial* with the factors Group, Sigh/nonsigh, and Position (1, 2, 3) showed three interactions involving Group. A Group × Sigh/nonsigh interaction for pCO_2 [$F(2,40) = 3.65$, $p < .04$] resulted from a slower recovery after the sigh breath in PD patients. Post hoc tests demonstrated that in the three postsigh breaths together PD patients had lower pCO_2s than in the corresponding breaths from the nonsigh ensemble, whereas for GAD patients and control subjects this was not the case. For TV a significant three-way interaction [$F(4,94) = 2.85$, $p < .03$)] can be attributed to a failure of TVs in PD patients to recover after the sigh to nonsigh ensemble levels, unlike the other groups. Post hoc tests show that TV recovered in the pattern t + 1 > t + 3 for both GAD patients and control subjects, but not for PD patients. Minute volume showed a similar pattern, but the three-way interaction was only significant at a trend level [$F(4,94) = 2.26$, $p < .07$)].

Sigh/nonsigh × Position effects (disregarding Group) showed that breaths following sighs were different only for pCO_2 [$F(2,80) = 36.0$, $p < .0001$] and RR [$F(2,94) = 16.3$, $p < .0001$]. Post hoc tests confirmed what is apparent in Figure 3—namely, that breaths from sigh ensembles had lower pCO_2 in all positions than nonsigh ensembles, and that the sigh ensembles evinced an inequality with the pattern t + 1 < t + 2 < t + 3, whereas in the nonsigh ensembles all positions were equal. RR showed exactly the same pattern.

Ensemble Averages: Autonomic Effects

Analyses of variance that included all three groups, sigh and nonsigh breath-containing ensembles, and all seven ordinal positions of the ensembles showed no significant three-way interactions or other effects involving group for SC or HR. However, Sigh × Position interactions (not involving Group) were significant for all three variables (in each case, $p < .0001$). For SC, these effects stemmed from higher SC following sighs [Position × Sigh/nonsigh interaction, $F(2,80) = 4.01$, $p < .03$]. Skin conductance was higher at t + 1, t + 2, and t + 3, but although in sigh ensembles the pattern was t + 1 > t + 3, these three positions did not differ in nonsigh ensembles. Heart rate was higher for sigh (t0) than for corresponding nonsigh breaths [$F(1,47) = 123.27$, $p < .0001$]. Analysis of the three breaths preceding sighs found a Position × Sigh/nonsigh effect [$F(2,94) = 4.31$, $p < .02$]. At the t − 1 position HR was already higher in sigh ensembles than in nonsigh ensembles. Postsigh ensembles showed no significant effects.

Relationship between pCO_2 and Its Possible Determinants

Mean levels of pCO_2, MV and its components, TV and RR, and sigh frequency were calculated over all breaths of

each individual. For pooled subjects, only sigh frequency correlated significantly with pCO_2 [$r(43) = -.45$, $p < .002$]. The next highest correlation with pCO_2 was TV [$r(43) = -.28$, $p < .07$], followed by RR [$r(43) = .12$, ns] and MV [$r(43) = -.11$, ns]. Within the PD group there were no significant correlations, within the GAD group only TV was significant [$r(12) = -.69$, $p < .01$], and with the control subjects only sigh frequency [$r(17) = -.53$, $p = .03$]. In a stepwise multiple regression analysis of pooled subjects with pCO_2 as the dependent variable, sigh frequency was the first variable to be selected, with an F-to-enter of 10.6 ($p < .002$), and TV was the second, with an F-to-enter of only 1.09 ($p = .30$).

A reason for the importance of sighs in determining pCO_2 level may be the disproportionate pCO_2-lowering effect of greater TVs. We tested for this effect in our data by calculating within each subject for each breath the difference in end-tidal pCO_2 from nonsigh mean levels and comparing this difference with the difference in TV from nonsigh mean levels. To reduce irrelevant variance, pCO_2 differences were averaged over all TV differences falling within 4-mL ranges: 1) −115 to 0, 2) 0 to +115, 3) + 115 to +230, and 4) +230 to +345 (+345 mL being the average for sigh thresholds across groups). Analysis of variance showed no significant Group [$F(2,40) = 0.22$, $p > .8$] or Group × Range [$F(6,120) = 0.20$, $p > .9$] effects, but a significant Range effect [$F(3,120) = 9.87$, $p < .0002$]. The pooled group means (SDs) of pCO_2 differences were 0.12 mm Hg (0.40) for range 1, 0.01 (0.35) for range 2, −0.13 (0.56) for range 3, and a disproportionally greater drop of −0.60 (1.04) for range 4. Pairwise contrasts of successive ranges confirmed that pCO_2 differences differed only between the two highest ranges [$F(1,40) = 10.93$, $p < .003$], not between the others [p's $> .2$]. This indicates that a nonlinearity between TV increase and pCO_2 drop is apparent even below the sigh threshold.

Panickers versus Nonpanickers

Although the numbers of subjects are small, among the PD patients the six panickers were compared statistically to the 10 nonpanickers. Panickers did not differ from nonpanickers in sigh frequency, run length, or on any of the autocorrelation indices. Overall ANOVAs including all seven ordinal breath positions showed effects involving Group only for pCO_2 [Group × Sigh/nonsigh × Position, $F(6,72) = 3.95$, $p < .002$]. Follow-up ANOVAs located the differences in the presigh sequences. Means tests showed that pCO_2 was lower on the t − 1 breath for panickers than for 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. Significance patterns for sigh frequency and run length were unaltered. The patterns of significance for autocorrelation indices also remained largely the same, except for autocorrelation of tidal volume at lag 2 when sighs were not removed, which was no longer significantly lower in PD patients than in the other groups ($p < .07$). In the overall ANOVAs, three-way interactions for TV and RR remained significant, but not for pCO_2. Follow-up ANOVAs of TV and RR showed a loss of the Group effect for RR in nonsigh sequences, but no changes in the patterns of significance in ANOVAs of sigh, presigh, or post-sigh breaths. Patterns of means tests for these two variables were unaltered.

Restriction to Diagnostically Nonoverlapping Groups

Analyses were redone after excluding the three GAD patients with a history of PD and the three PD patients with current GAD. Significance patterns for sigh frequency and run length were unaltered. The patterns of significance for autocorrelation indices also largely remained the same, except for autocorrelation of tidal volume at lag 2 when sighs were not removed, which was no longer significantly lower in PD patients than in the other groups ($p < .07$). In the overall ANOVAs, previously significant three-way interactions (pCO_2, TV, and RR) remained significant. Follow-up ANOVAs for these variables did not change in their patterns of significance, except that for TV the postsigh three-way interaction was no longer significant. Patterns of means tests for postsigh pCO_2 and RR were unaltered.

Discussion

The distributions of individual TVs were positively skewed in all of our groups, with PD patients having a greater proportion of breaths at the positive extreme. Sequential dependencies of TVs were reduced in PD patients, indicating a shorter respiratory "memory" than that of other groups. For distinguishing PD patients from control subjects, the sigh definition taken from the literature of twice the normal TV was close to optimal. Our sequential analysis found that 80–90% of sighs were isolated; in most other cases only two occurred in succession, which was slightly more likely than expected from their base rate. Respiratory rates were also distributed differently in the anxious patients, with larger SDs and more positive skews.

Our first hypothesis, that in PD patients sigh breaths would be preceded by breaths with lower TV, lower MV,

and higher pCO_2, was disconfirmed. In fact, there was no evidence for a triggering mechanism of this kind in any of our groups. That pCO_2 was not higher before sighs is consistent with a study of normal subjects at rest (Patil et al 1990). Our second hypothesis, that PD patients would show higher chemoreceptor gain, was also disconfirmed. Higher gain, at least for peripheral chemoreceptors (Bellville et al 1979), would have been indicated by a rapid rebound in pCO_2 and tidal volume (if respiration rate was constant), but PD patients showed the opposite. After-sigh pCO_2 levels at $t + 2$ and $t + 3$ were farther below corresponding nonsigh values in PD patients than in control subjects, a sign of lower gain. Slow recovery of pCO_2 was consistent with the pattern for TV: the after-sigh TVs did not return to nonsigh levels at $t + 2$ and $t + 3$ in PD patients, whereas they did in control subjects. Minute volume followed the same pattern as TV, but only at trend levels of statistical significance, most likely because as a composite of two direct measures, RR and TV, its error variance would be higher than the variance of either of its component measures. Recovery in RR did not differ between groups.

These results are incompatible with one version of the suffocation alarm but compatible with a revised version. The triggering mechanism for sighs may still be associated with suffocation stimuli, but lies outside the usual homeostatic control loops for CO_2 regulation. For example, the trigger could operate by abruptly changing the set point of the pCO_2 regulatory mechanism. In PD patients this trigger may be abnormally frequent and cause a sustained lowering of the set point, resulting in the tonically lower pCO_2 levels in both sigh and nonsigh ensembles. This would be consistent with lower rather than higher gain of the chemoreceptor in PD patients. Whether the trigger is associated with sympathetic discharge is unclear: HR is higher before the sighs, but SC does not rise until afterwards. Of course, it is also possible that not all sighs were triggered in the same way and that, in PD especially, a mixture of at least two types of sighs occurred. However, we failed to find group differences in within-subject variability of postsigh pCO_2 recovery, a possible indicator of heterogeneity of sighs.

Whatever the exact triggering mechanism, the pattern of slower recovery of pCO_2 and tidal volume after sighs in PD patients is consistent with a hypothesized greater respiratory after-discharge in this group (Folgering 1999). Short-term potentiation or after-discharge refers to a persistence in altered breathing beyond when the stimulus for the alteration has ceased, presumably originating in neural networks close to basic respiratory centers in vertebrates. This phenomenon may underlie both our results here and the slow pCO_2 recovery after several minutes of voluntary hyperventilation in PD patients (Wilhelm et al, in press). On the other hand, decreased respiratory "memory" in PD patients (based on the entire sequences of TVs) could be interpreted to mean that after-discharge was reduced in this group.

Our findings raise many additional questions, which are not possible to answer fully from our data set:

1. Are the findings specific to PD? Generalized anxiety disorder patients show intermediate values between PD patients and control subjects on certain measures. The reason for this is uncertain because both groups reported the same amounts of state anxiety during testing, and elimination of overlapping diagnoses had little effect on the results.
2. Are the findings a direct reflection of panic attacks? That seems unlikely because eliminating patients with attacks had little influence on the results, but the small number of attacks weakens the statistical power of our comparisons.
3. Is hypocapnia a cause or effect of sighing? Our correlational analysis cannot distinguish cause and effect, but certain kinds of longitudinal data (e.g., from 24-hour monitoring) or systematic experimental manipulation of pCO_2 and sighing might help.
4. What is the influence of our setting? Quiet sitting is not necessarily relaxing for PD patients or other anxious patients, who may be less anxious when they are distracted from their bodily sensations and other worries, but without data outside the laboratory, we are uncertain to what extent quiet sitting is an anxiety provocation. The breath holding procedure 10 min before quiet sitting may have fueled suffocation anxieties and respiratory changes in PD patients, although their subjective reports of anxiety before and after breath holding do not support that (for additional discussion, see Wilhelm et al 2001).

In spite of these limitations, our results are important for understanding the mechanism of the resting hypocapnia repeatedly observed in PD patients (Hegel and Ferguson 1997; Munjack et al 1993; Rapee 1986). Hypocapnia is almost certainly a result of hyperventilation, which in the mind of clinicians usually conjures up the image of heavy breathing, acutely anxious emergency room patients. However, as our regression analysis showed, in quietly sitting individuals pCO_2 is more closely related to an increased frequency of sporadic sighs than to sustained increases in ventilation, as was the case during recovery from voluntary hyperventilation in another study (Wilhelm et al, in press). Larger breaths contribute disproportionally to lowering pCO_2, probably because in them the ratio of outside air to dead-space air is higher. Thus, PD patients had three reasons for lower mean pCO_2 than other groups: the frequency of their sighs was higher, the

magnitude of their sighs was greater, and their pCO_2 returned to presigh levels slower, as if the compensation presumably mediated by peripheral chemoreceptor response was less brisk. Thus, whatever mechanisms predominate, sighing respiration is an important characteristic of PD patients even when they are not exposed to immediate anxiety provocations.

This research was supported by the Department of Veterans Affairs and the National Institutes of Health (Grant No. MH56094).

The authors thank Drs. Donald F. Klein and James L. Abelson for their helpful discussions of an earlier draft of the manuscript.

References

Abelson JL, Weg JG, Nesse RM, Curtis GC (2001): Persistent respiratory irregularity in patients with panic disorder. *Biol Psychiatry* 49:588–595.

Bellville JW, Whipp BJ, Kaufman RD, Swanson GD, Aqleh KA, Wiberg DM (1979): Central and peripheral chemoreflex loop gain in normal and carotid body-resected subjects. *J Appl Physiol* 46:843–853.

Finesinger JE (1943): The spirogram in certain psychiatric disorders. *Am J Psychiatry* 100:159–169.

Folgering H (1999): The hyperventilation syndrome. In: Altose MD, Kawakami Y, editors. *Control of Breathing in Health and Disease.* New York: Marcel Dekker, 633–660.

Hegel MT, Ferguson RJ (1997): Psychophysiological assessment of respiratory function in panic disorder: Evidence for a hyperventilation subtype. *Psychosom Med* 59:224–230.

Khoo MC, Marmarelis VZ (1989): Estimation of peripheral chemoreflex gain from spontaneous sigh responses. *Ann Biomed Eng* 17:557–570.

Klein DF (1992): False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. *Arch Gen Psychiatry* 50:306–317.

Ley R (1989): Dyspneic-fear and catastrophic cognitions in hyperventilatory panic attacks. *Behav Res Ther* 27:549–554.

Liebowitz MR, Fyer AJ, Gorman JM, et al (1984): Lactate provocation of panic attacks. I. Clinical and behavioral findings. *Arch Gen Psychiatry* 41:764–770.

Lieske SP, Thoby-Brisson M, Telgkamp P, Ramirez JM (2000): Reconfiguration of the neural network controlling multiple breathing patterns: Eupnea, sighs and gasps. *Nat Neurosci* 3:600–607.

Lousberg H, Griez E, van den Hout MA (1988): Carbon dioxide chemosensitivity in panic disorder. *Acta Psychiatr Scand* 77:214–218.

Munjack DJ, Brown RA, McDowell DE (1993): Existence of hyperventilation in Panic Disorder with and without Agoraphobia, GAD, and normals: Implications for a cognitive theory of panic. *J Anxiety Disord* 7:37–48.

Pain MCF, Biddle N, Tiller JWG (1988): Panic disorder, the ventilatory response to carbon dioxide and respiratory variables. *Psychosom Med* 50:541–548.

Patil CP, Saunders KB, Sayers BM (1990): Timing of deep breaths during rest and light exercise in man. *Clin Sci (Colch)* 78:573–578.

Rapee R (1986): Differential response to hyperventilation in panic disorder and generalized anxiety disorder. *J Abnorm Psychol* 95:24–28.

Roth WT, Wilhelm FH, Trabert W (1998): Voluntary breath holding in panic and generalized anxiety disorders. *Psychosom Med* 60:671–679.

Sanderson WC, Rapee RM, Barlow DH (1989): The influence of an illusion of control on panic attacks induced via inhalation of 5.5% carbon dioxide enriched air. *Arch Gen Psychiatry* 46:157–162.

Schwartz GE, Goetz RR, Klein DF, Endicott J, Gorman JM (1996): Tidal volume of respiration and "sighing" as indicators of breathing irregularities in panic disorder patients. *Anxiety* 2:145–148.

Tobin M, Yang K, Jubran A, Lodato R (1995): Interrelationship of breath components in neighboring breaths of normal eupneic subjects. *Am J Respir Crit Care Med* 152:1967–1976.

Tobin MJ, Chadha TS, Jenouri G, Birch JS, Gazeroglu HB, Sackner MA (1983): Breathing patterns. 2. Diseased subjects. *Chest* 84:286–294.

Wilhelm FH, Gerlach AL, Roth WT (in press): Slow recovery from voluntary hyperventilation in panic disorder. *Psychosom Med*.

Wilhelm FH, Trabert W, Roth WT (2001): Physiologic instability in panic disorder and generalized anxiety disorder. *Biol Psychiatry* 49:596–605.