

# Somatic Symptoms and Physiologic Responses in Generalized Anxiety Disorder and Panic Disorder

## *An Ambulatory Monitor Study*

Rudolf Hoehn-Saric, MD; Daniel R. McLeod, PhD; Frank Funderburk, PhD; Pamela Kowalski

**Background:** Physiologic responses of patients with anxiety disorders to everyday events are poorly understood.

**Objective:** To compare self-reports and physiologic recordings in patients with panic disorder (PD), patients with generalized anxiety disorder (GAD), and nonanxious controls during daily activities.

**Design:** Participants underwent four 6-hour recording sessions during daily activities while wearing an ambulatory monitor. Physiologic and subjective data were recorded every 30 minutes and during subject-signaled periods of increased anxiety or tension or panic attack.

**Setting:** Participants' everyday environment.

**Participants:** Twenty-six patients with PD and 40 with GAD, both without substantial comorbidity, and 24 controls.

**Interventions:** Recordings obtained during everyday activities.

**Main Outcome Measures:** Recordings of heart inter-beat intervals, skin conductance levels, respirations, motion, and ratings of subjective somatic symptoms and tension or anxiety.

**Results:** Patients with anxiety disorders rated higher on psychic and somatic anxiety symptoms than did controls. Common to both anxiety disorders was diminished autonomic flexibility that manifested itself throughout the day, accompanied by less precise perception of bodily states. The main differences between patients with PD and GAD were a heightened sensitivity to body sensations and more frequent button presses. There also was a trend toward heightened basal arousal in patients with PD, manifesting itself in a faster heart rate throughout the day.

**Conclusions:** Patients with PD or GAD are more sensitive to bodily changes than nonanxious individuals, and patients with PD are more sensitive than those with GAD. Patients with PD experience more frequent distress than those with GAD and controls, but their physiologic responses are comparable in intensity. The findings suggest that the perception of panic attacks reflects central rather than peripheral responses. The diminished autonomic flexibility observed in both anxiety conditions may result from dysfunctional information processing during heightened anxiety that fails to discriminate between anxiety-related and neutral inputs.

*Arch Gen Psychiatry. 2004;61:913-921*

**A**NXIETY IS A BIOLOGICAL warning system that prepares us for action. Considering subjective and objective body reactions observed in nonanxious individuals during acute stress,<sup>1-4</sup> it is reasonable to assume that patients with chronic anxiety disorders exhibit physiologic hyperarousal at rest or heightened physiologic responses to stressors. This, however, is not uniformly the case. The most consistent finding in patients with anxiety is increased muscle tension.<sup>1</sup> Autonomic changes are found less consistently. Our group<sup>5</sup> found that patients with generalized anxiety disorder (GAD) showed nor-

mal heart rate, skin conductance, and respiration values while at rest. During laboratory stress, patients with GAD actually had a lower skin conductance response than controls.<sup>5</sup> In some other studies,<sup>6-8</sup> patients with GAD exhibited an increased heart rate and decreased cardiac vagal tone during rest and during mental stress.

Similarly, in some studies, patients with panic disorder (PD) exhibited normal heart rate, skin conductance, and respiration values while at rest, whereas other studies found increases in those physiologic functions.<sup>1,9,10</sup> The most consistent laboratory finding in patients with chronic anxiety was diminished physi-

*From the Department of Psychiatry, The Johns Hopkins Medical Institutions, Baltimore, Md.*

ologic flexibility (DPF), namely, a diminished range or variability of physiologic responses to stressors found in most,<sup>1,10-13</sup> but not all,<sup>14</sup> studies.

Moreover, most studies of patients with anxiety rely on self-reports of somatic symptoms, despite the fact that somatic manifestations often correlate poorly with physiologic states and reactions, and cannot be taken at face value.<sup>15</sup>

Most physiologic studies have been conducted in the laboratory, which provides a controlled environment and permits multiple simultaneous recordings but rarely reflects stressors experienced in everyday situations. Therefore, physiologic states and responses in laboratory studies may differ from those experienced by patients in real life.

The aim of this study is to measure self-reports and physiologic states in patients with GAD, patients with PD, and controls in their natural environment using an ambulatory monitor. We are interested in how these 3 groups differ while they are not anxious, in their responses to stress or panic attacks, and in the relationship between experienced states and actual physiologic responses. We are also interested in determining whether diminished autonomic flexibility occurs in natural settings and represents an altered physiologic response pattern in patients with chronic anxiety or whether it represents a laboratory artifact due to diminished attention to tasks that seem irrelevant to the anxious patient.

## METHODS

### PARTICIPANTS

A total of 113 individuals, consisting of physically healthy patients with GAD or PD and volunteers without a psychiatric disorder (controls), were recruited by advertising and gave informed consent to participate in the study. *Structured Clinical Interview for DSM-IV* criteria<sup>16</sup> were used to confirm the diagnoses, which, in case of doubt, were reviewed by a second investigator. All other psychiatric disorders, including substance abuse, were excluded, except mild specific phobias that did not interfere with the participant's functioning. A physical examination, including a urine toxicology screen, was performed during the initial screening. All participants had to abstain from medications that affect the central and autonomic nervous systems for at least 2 weeks before entering and during the study. To be included in the study, patients with GAD and PD were required to score 38 or greater on the trait scale of the State-Trait Anxiety Inventory<sup>17</sup> and 18 or more on the Hamilton Anxiety Rating Scale (HAM-A).<sup>18</sup> Patients with PD had to have at least 1 panic attack per week during the 4 weeks before testing. On entry into the study, participants also completed the Beck Depression Inventory,<sup>19</sup> the Sheehan Disability Scale,<sup>20</sup> the Barsky Amplification Scale,<sup>21</sup> and the Body Sensations Questionnaire.<sup>22</sup> Participants reported that they engaged in moderate daily physical activities.

The study sample was predominantly female (76%), with a mean age of 36 years (range, 19-55 years). Of the 90 participants who provided usable data, 24 were controls, 40 were diagnosed as having GAD, and 26 were diagnosed as having PD. More patients with GAD were recruited because we were also interested in patients with high vs low levels of cardiac symptoms.<sup>23</sup> In this article we compare the entire GAD group with the other 2 groups. The control group consisted of 17 whites, 3 African Americans, and 4 Asian Americans. The GAD group

consisted of 36 whites, 2 African Americans, 1 Hispanic, and 1 Asian American. The PD group consisted of 23 whites and 3 African Americans. As compensation, participants with an anxiety disorder were given free treatment after completion of the study, and controls were paid.

### DATA COLLECTION PROCEDURES

All participants attended a training session before actual assessment. They wore the ambulatory monitoring device while sitting in a reclining chair. For a half hour, participants were acclimated to the physiologic monitoring equipment and were trained to complete the rating forms. Subsequently, for 4 weekdays, they wore the ambulatory monitor and rated themselves on various scales for at least 6 hours between 9 AM and 5 PM while pursuing their usual daily activities.

### Self-report Assessment Scales

On study days the participants were required to provide information on self-report assessment forms at 30-minute intervals throughout the day. The Daily Rating Form allowed participants to rate the severity of symptoms commonly experienced during heightened anxiety on a scale from 0 ("absolutely none") to 100 ("as bad as it could possibly be"). Symptoms consisted of severity of "rapid heart beat or palpitations," "sweating," "difficulty breathing normally," "feeling tense," and "worrying." A 5-point scale, asking, "How nervous or upset are you now?" with the response choices of "not at all" to "extremely," allowed participants to rate their level of tension or anxiety while they rated the symptoms listed on the Daily Rating Form. The Physical Activity Level Form allowed participants to rate their level of activity at a particular time as "low," "mild," "moderate," or "high."

### Physiologic Measures

Physiologic measures were monitored continuously throughout the test days using an ambulatory monitoring device described by Thakor et al.<sup>24</sup> The monitor was placed in a carrying case that had shoulder and waist straps. The key physiologic measures of heart interbeat interval (IBI), skin conductance level, and respiration rate were obtained, along with the contextual variables of ambient temperature and activity. Ambient temperature was measured so as not to attribute changes in temperature that affect physiologic states, including skin conductance, to changes in an emotional state. Measures of physical activity levels provide an indicator of when autonomic changes should be attributed to physical activity. Heart IBI and breathing were measured using standard electrocardiographic electrodes attached to the sides of the chest. Skin conductance was measured using silver and silver chloride electrodes attached to 2 fingers of the nondominant hand. For skin conductance, a Unibase (Parke-Davis, New York, NY) and isotonic sodium chloride solution preparation was used as the electrolyte,<sup>25</sup> and the fingers were individually wrapped in self-adhesive gauze. Adhesive disks were used to allow skin exposure to the electrodes of exactly 1 cm in diameter. Activity level and ambient temperature were measured by sensors located within the ambulatory monitoring device. Participants were expected to wear the monitor for 8 hours each day, but technical problems caused data loss for many participants in the latter part of the day, so a 6-hour period was established as the standard for the study. The device automatically stored data in 6-minute epochs every 30 minutes. At each recording epoch, the monitor emitted a beep to alert the person who was wearing it that subjective ratings should be completed. In addition to this routine monitoring every 30 minutes, a button was available on the device

to allow participants to signal the occurrence of other important events. In this study, patients with GAD and controls were asked to press the button to indicate a "stressful occurrence." To avoid possible confusion between panic attacks and non-panic anxiety, patients with PD were asked to press the button only to indicate a panic attack but not a stressful occurrence. Physiologic data for the 3 minutes before and the 3 minutes after the button press were automatically stored. Pressing the button also produced an audible beep that served to cue the participants to complete the subjective data forms.

Heart IBI was measured 800 times per second; skin conductance, 4 times per second; and respiration, 10 times per second. Activity level and ambient temperature were stored once per second and once per minute, respectively. At the end of the recording time, the data were transferred to a personal computer for storage and statistical analysis. Data available for analysis included up to 16 epochs per participant session. Twelve 6-minute epochs were available for the routine sampling at 30-minute intervals during the session. Additional 6-minute epochs were allocated for measuring the physiologic status surrounding each button-press event reported by the participant.

## DATA ANALYSIS

### Overall Daily Effects

Analyses of overall daily effects focused on data obtained on the first day of the study. Independent analyses for the physiologic and subjective variables were undertaken using the statistical package BMDP-5V (Statistical Software Inc, Los Angeles, Calif), as required for an unbalanced repeated-measures model with structured covariance matrices.<sup>26-28</sup> Each analysis predicted the dependent variable (D) as a function of group membership, measurement occasion (recording epoch), and the interaction between these factors. The general form of the model was as follows:  $D = \text{Status} + \text{Time} + [\text{Status} \times \text{Time}]$ . The analysis assumed a first-order autoregressive within-subject covariance matrix. A maximum likelihood method was used to estimate parameters. Missing data were computed based on the estimated conditional mean of the missing response, given the values of the responses that were present. "Status" reflected the diagnostic category of the participant, whereas "time" reflected the average of the dependent variable during successive measurement occasions throughout the day. The first 12 measurement occasions of the daily session were used in these analyses.

### Analysis of Response to Stress or Panic

Participants in the 3 diagnostic groups who reported stress (or panic for the PD group) were examined in more detail to determine whether differences in response to stress were evident. Any stress period during the experimental sessions was included in the analysis, so some participants were represented by more than 1 data point. The unbalanced repeated-measures approach used for the analysis, implemented through BMDP-5V, took this lack of independence into account. Diagnostic group was a between-group factor, whereas the repeated-measure factor was time in reference to the report of stress (before, during, and after the button press).

### Relation Between Subjective and Physiologic Variables

The relation between objective and subjective responses for the 3 diagnostic groups was examined for measures of basal level

(daily average, not including button-press periods) and change due to stress (as indicated by the button press). A hierarchical set regression approach<sup>29</sup> was used. This approach investigated the relationship between the objective level of physiologic activity and the subject's report of the subjective state usually associated with that response. In these analyses, the subjective measure was considered the dependent measure, and the physiologic and diagnostic variables were regarded as predictors. Between-group differences were found in age, and this variable was used as a covariate in all analyses. The statistical package BMDP-2R (Statistical Software Inc) was used to perform the analyses.

Variables were forced into the regression in sets in the following order: age, group membership/physiologic response, linear interactions with group, and quadratic interactions with group. Interaction terms were carried by product variables as a function of their order of entry into the equation. The primary purpose of these analyses was to evaluate whether the diagnostic variable modified the nature of the relationship between physiologic level or physiologic change (for stress response) and the individual's report of the associated subjective variable.

## RESULTS

Demographic characteristics of the PD, GAD, and control groups are given in **Table 1**. Race and sex distributions did not differ as a function of diagnostic category, but control subjects were younger on average than those diagnosed as having GAD or PD. No interactions between diagnostic groups and sex were found. Both anxiety groups rated higher than controls on the total HAM-A, the cardiovascular symptoms item of the HAM-A, the state and trait scales of the State-Trait Anxiety Inventory, all items of the Sheehan Disability Scale, the Barsky Amplification Scale, and the Body Sensations Questionnaire. The PD group differed from the GAD group on the total HAM-A, the cardiovascular symptoms item of the HAM-A, and the Body Sensations Questionnaire.

### DAILY CHANGES DURING MONITORING SESSIONS

**Table 2** summarizes the significant effects during the first daily monitoring session. Responses on all of the subjective measures showed significant differences between groups, as did the physiologic measures of mean IBI, IBI variance, and skin conductance variance. In general, the analyses distinguished the participants with anxiety disorders from the controls. According to Mann-Whitney post hoc comparisons, both anxiety groups rated themselves higher than the controls on rapid heart beat, sweating, difficulty breathing, feeling tense, and worry; however, the anxiety groups did not differ from each other.

These findings were consistent with orthogonal contrasts, performed as part of the overall analysis comparing the physiologic measures of control subjects with those of patients with GAD and PD. The following results were obtained: mean heart rate was lower (IBI was greater) in controls ( $z = 1.89$ ;  $P = .06$ ), but IBI variance ( $z = 2.74$ ;  $P = .006$ ) and skin conductance variance ( $z = 2.87$ ;  $P = .004$ ) were greater in controls.

**Table 1. Demographic Characteristics of 90 Study Participants\***

	Panic Group (n = 26)	GAD Group (n = 40)	Controls (n = 24)
Age	36.1 ± 8.4	39.6 ± 9.2	31.6 ± 7.7†
Sex, %			
M	15.4	27.5	29.2
F	84.6	72.5	70.8
HAM-A score			
Total	27.6 ± 5.5	24.2 ± 4.0‡	2.3 ± 1.7§
Cardiovascular symptoms	1.9 ± 0.3	1.5 ± 0.5	1.0 ± 0.0¶
STAI trait scale score	50.75 ± 7.6	54.71 ± 6.0	30.60 ± 4.1¶
Sheehan Disability Scale score			
Work	4.96 ± 3.2	4.89 ± 2.7	0.74 ± 1.2¶
Social	5.20 ± 2.4	5.14 ± 2.9	0.70 ± 1.4¶
Family	4.33 ± 2.4	5.27 ± 2.8	0.63 ± 1.4¶
Barsky Amplification Scale score	30.08 ± 7.5	29.10 ± 6.1	22.92 ± 5.5¶
Body Sensations Questionnaire score	37.12 ± 16.7	22.67 ± 12.0#	14.77 ± 15.4**††
STAI state scale score	51.5 ± 8.1	54.4 ± 9.3	29.4 ± 4.7¶

Abbreviations: GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; STAI, State-Trait Anxiety Inventory.

\*Data are given as mean ± SD, except where noted otherwise.

†P<.05, panic and GAD>controls.

‡P<.01, panic>GAD.

§P<.01, panic and GAD>controls.

||P<.05, panic>GAD.

¶P<.001, panic and GAD>controls.

#P<.001, panic>GAD.

\*\*P<.001, panic>controls.

††P<.03, GAD>controls.

**Table 2. Summary of Overall Responses Across the First Day for Each Significant Dependent Variable\***

	Panic Group	GAD Group	Controls	Group		Time		Group × Time	
				χ <sup>2</sup> <sub>2</sub>	P Value	χ <sup>2</sup> <sub>9</sub>	P Value	χ <sup>2</sup> <sub>18</sub>	P Value
Rapid heart beat	6.5 ± 7.6	8.2 ± 9.0	1.4 ± 3.1††	19.8	<.001	4.2	NS	13.4	NS
Sweating	4.5 ± 6.7	3.5 ± 5.0	0.8 ± 2.4‡§	9.0	.01	14.1	NS	21.4	NS
Difficulty breathing	3.01 ± 5.8	2.5 ± 5.4	0.5 ± 2.1  ¶	6.2	.04	13.3	NS	14.7	NS
Feeling tense	19.0 ± 17.2	19.0 ± 17.0	3.1 ± 6.7‡§	25.5	<.001	13.0	NS	41.6	.001
Worrying	17.1 ± 19.4	18.1 ± 17.8	1.7 ± 3.9‡§	22.1	<.001	13.0	NS	29.4	.04
Mean IBI	687.5 ± 79.8	716.1 ± 85.4	736.9 ± 95.5	5.1	.07	13.2	NS	20.2	NS
IBI variance	1245.4 ± 935.0	1309.4 ± 975.0	2030.9 ± 1965.8	5.9	.05	8.2	NS	12.9	NS
Skin conductance variance	0.002 ± 0.001	0.002 ± 0.001	0.003 ± 0.004	8.3	.02	14.5	NS	30.0	.04

Abbreviations: GAD, generalized anxiety disorder; IBI, interbeat interval; NS, not significant.

\*Data are given as mean ± SD.

†P<.01, panic>controls.

‡P<.001, GAD>controls, Mann-Whitney post hoc comparisons.

§P<.001, panic>controls, Mann-Whitney post hoc comparisons.

||P<.05, panic>controls, Mann-Whitney post hoc comparisons.

¶P<.05, GAD>controls, Mann-Whitney post hoc comparisons.

### DIFFERENCES BETWEEN GROUPS WHEN STRESS OR PANIC WAS REPORTED

Participants who reported stress or panic during the study did not differ in terms of age. However, the PD subgroup reporting panic attacks was predominantly female (88% women), whereas the control subgroup reporting stress was predominantly male (71% men). The GAD subgroup reporting stress was equally divided (50% women).

**Table 3** gives means and standard deviations for subjective responses that showed a significant difference between the last rating before the button press and during the button press indicating stress or anxiety or,

in patients with PD, a panic attack. Patients with PD showed increased response at the time of button press compared with the preceding recording for difficulty breathing, rapid heart rate, sweating, feeling tense, and worry. The GAD group showed an increase only for rapid heart rate and feeling tense. The control group showed no significant changes. None of the groups showed differences between ratings obtained before and after the button press. When the groups were compared for difference in scores between baseline and button press, the PD group differed from the control group in rapid heart beat, sweating, difficulty breathing, and feeling tense, whereas the GAD group differed from the control group only in rapid heart beat. The PD group differed from the

**Table 3. Subjective Response Ratings of Participants Who Pressed the Button During Stress (Control and GAD Groups) or Panic (Panic Group)<sup>a</sup>**

Response and Button Press Timing	Panic Group	GAD Group	Controls	Group		Time		Group × Time	
				χ <sup>2</sup>	P Value	χ <sup>2</sup>	P Value	χ <sup>2</sup>	P Value
Rapid heart rate				0.6	NS	34.2	<.001	26.2	<.001
Before	12.9 ± 16.8	12.7 ± 16.9	25.7 ± 37.4						
During	40.3 ± 30.8 <sup>b</sup>	32.0 ± 20.3 <sup>c</sup>	36.0 ± 40.4 <sup>d,e</sup>						
After	11.9 ± 17.0	16.0 ± 16.6	28.6 ± 36.7						
Sweating				9.9	.007	17.8	<.001	45.8	<.001
Before	10.6 ± 21.1	11.0 ± 3.2	21.4 ± 33.4						
During	32.5 ± 21.1 <sup>b</sup>	25.0 ± 4.3 <sup>f</sup>	30.0 ± 36.7 <sup>d</sup>						
After	11.1 ± 6.3	33.0 ± 5.0	21.4 ± 33.4						
Difficulty breathing				12.1	.002	8.7	.01	19.3	.001
Before	5.0 ± 14.6	9.0 ± 2.0	15.7 ± 23.7						
During	29.7 ± 26.9 <sup>g</sup>	10.0 ± 3.2	22.0 ± 25.9 <sup>h</sup>						
After	10.8 ± 19.1	0.0 ± 0.0	15.7 ± 23.7						
Feeling tense				4.1	NS	29.4	<.001	29.7	<.001
Before	24.3 ± 19.8	18.6 ± 20.0	28.6 ± 36.2						
During	62.2 ± 33.0 <sup>i</sup>	34.5 ± 21.9 <sup>k</sup>	55.0 ± 28.9 <sup>l</sup>						
After	27.2 ± 20.0	26.5 ± 18.0	31.4 ± 36.2						
Worrying				3.3	NS	26.6	<.001	29.8	<.001
Before	21.4 ± 20.7	20.0 ± 24.0	22.9 ± 27.5						
During	64.7 ± 33.5 <sup>b</sup>	30.5 ± 25.2 <sup>m</sup>	42.0 ± 21.7 <sup>d</sup>						
After	21.8 ± 17.9	22.0 ± 21.8	31.4 ± 27.3						

Abbreviations: GAD, generalized anxiety disorder; NS, not significant.

<sup>a</sup>Responses were measured during the 6 minutes a half hour before the button press, during the 6 minutes surrounding the button press, and during the 6 minutes a half hour after the button press. Data are given as mean ± SD. Statistical differences between groups are shown for differences between button press and the last rating before the button press.

<sup>b</sup>P<.02, panic.

<sup>c</sup>P<.002, GAD.

<sup>d</sup>P<.02, panic>controls.

<sup>e</sup>P<.002, GAD>controls.

<sup>f</sup>P<.02, panic>GAD.

<sup>g</sup>P<.05, panic.

<sup>h</sup>P<.05, panic>controls.

<sup>i</sup>P<.004, panic.

<sup>j</sup>P<.05, panic>GAD.

<sup>k</sup>P<.05, GAD.

<sup>l</sup>P<.008, panic>controls.

<sup>m</sup>P<.03, panic>GAD.

GAD group in sweating, feeling tense, and worry, along with a tendency toward difficulty breathing. There were no statistically significant differences in measures of skin conductance, heart rate, or respiration. In the control group, 75% of button presses were accompanied by an increase in heart rate; in the GAD group, 71% of button presses were accompanied by an increase in heart rate; and in the PD group, 74% of button presses were accompanied by an increase in heart rate.

In addition, an examination of button-press data from all 4 days of the experiment revealed between-group differences in the frequency of button pressing (**Table 4**). During the experiment, 29% of controls (n=7) indicated at least 1 stressful period compared with 42% of patients with GAD (n=17) and 65% of patients with PD (n=17) who experienced a full-blown panic attack at least 1 time during the study (χ<sup>2</sup>=6.87; P=.03).

#### RELATION BETWEEN SUBJECTIVE AND PHYSIOLOGIC DATA

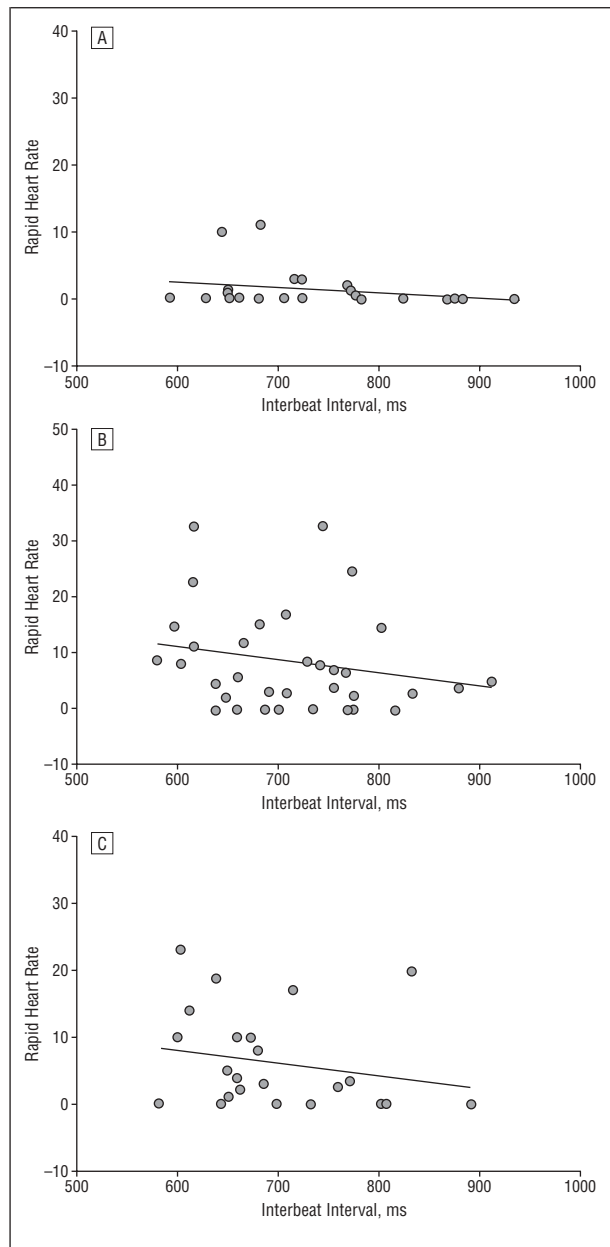
Relations between subjective and physiologic data were examined using hierarchical regression analysis and data from the basal period for mean IBI and mean skin con-

**Table 4. Frequency of at Least 1 Button Press During the Experimental Sessions by Diagnostic Group**

Button Press	Controls	GAD Group	Panic Disorder Group	Total
Yes	7	17	17	41
No	17	23	9	49
<b>Total</b>	<b>24</b>	<b>40</b>	<b>26</b>	<b>90</b>

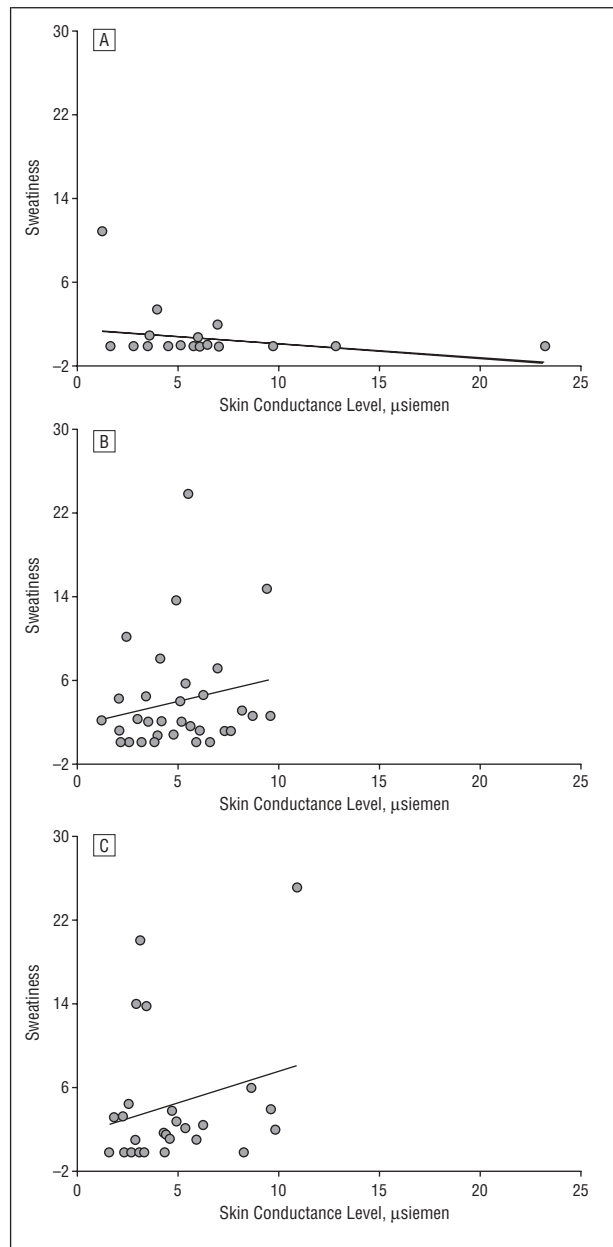
Abbreviation: GAD, generalized anxiety disorder.

ductance level. **Figure 1** and **Figure 2** illustrate how the relation between basal objective and subjective measures differed as a function of diagnostic category. An overall negative linear relationship was identified between mean IBI (inversely related to heart rate) and perception of rapid heart rate (F<sub>2,78</sub>=5.62; R<sup>2</sup> inc=0.121; P=.006), but this overall effect was more pronounced for controls than for individuals with PD or GAD (F<sub>1,79</sub>=10.3; R<sup>2</sup> inc=0.111; P=.001) (Figure 1). Thus, although there was a general trend in all participants to associate lower IBI values with a subjective report of a more rapid heart beat, the trend was stronger in nonanxious control sub-



**Figure 1.** Subjective estimates of rapid heart rate vs recorded mean interbeat interval in nonanxious controls (A), patients with generalized anxiety disorder (B), and patients with panic disorder (C). Data points represent the mean values across a 6-hour period in the absence of a button press. Estimates of rapid heart rate were rated on a scale from 1 to 100.

jects. This finding suggests that, overall, the participants in the anxiety disorder groups were less “responsive,” as expressed by the slope of subjective vs physiologic relationships, to differences in the IBI than were nonanxious controls. Again using data from the basal period, the relation between skin conductance level and perceived sweating was statistically significantly different among the diagnostic groups (Figure 2). The controls associated more accurately the 2 conditions ( $F_{2,77}=5.15$ ;  $R^2 \text{ inc}=0.112$ ;  $P=.008$ ). No statistically significant main effects or interactions were found in the analysis of the relationship between basal respiration and reported difficulty of breathing. Patients in each anxiety disorder group differed significantly more among themselves in



**Figure 2.** Subjective estimates of sweatiness vs recorded mean skin conductance level in nonanxious controls (A), patients with generalized anxiety disorder (B), and patients with panic disorder (C). Data points represent the mean values across a 6-hour period in the absence of a button press. Estimates of sweatiness were rated on a scale from 1 to 100.

the accuracy of estimation of bodily functions than did controls.

#### COMMENT

This study described and compared the subjective and physiologic responses of patients with GAD, patients with PD, and controls who wore a specially constructed ambulatory monitor during daily activities. For calculating subjective and physiologic states when not feeling tense or anxious, we used the data from the first day’s recording because they were most complete. For calculating changes when stressed, we included button presses and the recording of the preceding automatic half-hour re-

cording from all 4 recording days. Because a button press can occur at any time after the last 6-minute recording period, the time between the 2 recordings, without overlapping, could have been 27 minutes or less.

### RESPONSES OF PARTICIPANTS WHEN NOT RECORDING ANXIETY OR STRESS

Patients with GAD and PD rated themselves higher on psychic and somatic anxiety, on disability scales, and on sensitivity to body sensations than controls. However, patients with PD and GAD differed little from each other on self-ratings, except on the Body Sensations Questionnaire, where patients with PD rated higher than patients with GAD, indicating heightened concern with bodily functions. This finding is consistent with the idea that patients with PD interpret physical sensations as dangerous and patients with GAD interpret them as anxiety but is at variance with findings from previous studies<sup>30-32</sup> indicating that patients with PD reported significantly more autonomic symptoms than patients with GAD. There are several possible explanations for these differences. Patients with GAD and PD are not homogenous groups and may vary considerably in type and severity of physical symptoms. Moreover, preoccupation with somatic symptoms may not relate to the degree of physiologic change.<sup>15</sup> Patients also may have different anchoring points of severity for symptoms,<sup>33</sup> and self-ratings may depend on the instructions given to the participant.<sup>34</sup>

Patients with PD, patients with GAD, and controls showed little difference in their physiologic responses when not registering anxiety, except for a trend in patients with PD to have a faster heart rate throughout the day. This finding corresponds with results obtained in some, but not all, laboratory studies. Differences in the severity of PD may contribute to differences in heart rate. For example, Charney et al<sup>35</sup> found that physiologic responses to yohimbine challenge in patients with PD correlated with the average number of panic attacks. Another possibility is that patients with PD did less physical exercise than nonanxious subjects. Physical exercise affects the physiologic state of an individual.<sup>36</sup> However, our patients, by interview and by self-ratings while wearing the monitor, pursued normal daily activities that were comparable to those of the other groups. If the groups had differed significantly in physical condition, one would expect differences in their physiologic data, which was not the case. Our data suggest that patients with PD experienced not only heightened sensitivity to bodily sensations but slightly higher autonomic arousal levels than patients with GAD and controls. Respiration rate did not differentiate the groups, but the monitor recorded only frequency, not volume. Several studies<sup>37-39</sup> suggest respiratory irregularity and higher tidal volume in patients with PD that our recording device missed.

### DIMINISHED PHYSIOLOGIC FLEXIBILITY

The most prominent physiologic finding of this study was the decreased variance in heart IBI and skin conductance throughout the day in both anxiety groups compared with controls. Our group found DPF in the laboratory in pa-

tients with GAD,<sup>5</sup> patients with PD,<sup>40</sup> and patients with obsessive-compulsive disorder<sup>41</sup>; other laboratories confirmed these findings in patients with GAD<sup>8</sup> and PD.<sup>10,12</sup> Other studies found DPF in patients with phobic anxiety,<sup>42</sup> posttraumatic stress disorder,<sup>43</sup> depression,<sup>44</sup> premenstrual syndrome,<sup>45</sup> and alcoholism<sup>46</sup> and in individuals with high neuroticism or social maladjustment.<sup>3,47,48</sup> Furthermore, DPF manifests itself in anxious individuals as decreased catecholamine<sup>3,47</sup> and cortisol<sup>49-51</sup> excretion and in electroencephalographic responses to challenges.<sup>52,53</sup> Thus, diminished responsiveness to stressors is a nonspecific central and peripheral manifestation that accompanies prolonged anxiety or stress. There are several possible explanations for this phenomenon. First, DPF does not represent a "ceiling effect," as proposed by some investigators,<sup>53,54</sup> because baseline values of patients with chronic anxiety and their response to stressors do not often differ from those of nonanxious subjects. Constitutional factors, as seen in shy children,<sup>55</sup> may predispose individuals to DPF and anxiety disorders, but the developmental course and clinical implications of such possible effects are not well understood. Diminished physiologic flexibility may represent a partial but inadequate attempt by the body to adapt to the physiologic changes induced by chronic anxiety.<sup>56,57</sup> A psychological explanation is also plausible. Anxiety, particularly worry, preoccupies anxious individuals with internal events and diminishes their attention to stimuli that are unrelated to their pathologic condition.<sup>48,58</sup> Thayer and Lane<sup>59</sup> presented a model in which diminished cardiac vagal tone, manifesting itself in diminished heart beat variability, represents the peripheral manifestation of inadequate central inhibition of the autonomic system in anxious subjects; a high vagal tone is associated with greater behavioral flexibility. According to this model, the Central Autonomic Network, a functional unit that appears to support goal-directed behavior and adaptability, includes the anterior cingulate, the insular and ventromedial prefrontal cortices, the periaqueductal gray, and nuclei of the hypothalamus, the striatum, and the pontine regions. Its primary output system is mediated through the preganglionic sympathetic and parasympathetic neurons. The system interprets visceral, humoral, and environmental information and coordinates autonomic, endocrine, and behavioral responses to environmental challenges. Anxiety leads to inhibition of the parasympathetic system and to dominance of the sympathetic system, which manifests itself in decreased responsiveness of the cardiovascular system to rapid changes in environmental demands. Although their model may explain many physiologic response patterns, a change in cardiac vagal tone is not invariably associated with DPF. We did not find diminished vagal tone in patients with GAD (D.R.M. and R.H.-S., unpublished data, 2000), and other researchers have not found it in patients with PD<sup>60</sup> or in depression despite an increased heart rate.<sup>61</sup> Using functional magnetic resonance imaging, our group<sup>62</sup> found that patients with GAD exhibited strong BOLD responses in the prefrontal and limbic regions to statements that described a personal worry and to neutral statements. Reduction of anxiety with citalopram therapy led to weaker BOLD responses to both but particularly to neutral statements. These findings<sup>62,63</sup> suggest that during high anxiety, cerebral re-

sponses to stimuli become indiscriminate to the nature of the stimulus, leading to dysfunctional central processing of information. The indiscriminant responses to stimuli may lead to limited modulation of physiologic reactivity without necessarily involving the vagal system. Further clarifications of the biological function of DPF and its long-term effects on health are needed.<sup>59,64</sup>

#### RESPONSES TO A BUTTON PRESS INDICATING PANIC, ANXIETY, OR STRESS

At the time of button press, all 3 groups registered higher reports of rapid heart beat, sweating, difficulties breathing, feeling of tension, and worry. These increases were strongest in patients with PD and weakest in controls. The greatest increase in self-ratings was in difficulty breathing, which increased 6-fold. In addition, patients with PD pressed the button significantly more frequently (indicating a panic attack) than did patients with GAD and controls, although the latter groups were instructed to press the button whenever they felt tense or anxious. Thus, patients with PD experienced not only more severe but also more frequent anxiety.

Reports of physiologic changes during panic attacks indicate that marked, mild, or no physiologic changes may accompany attacks. Heart rate changes, recorded spontaneously in the laboratory or by ambulatory monitors during panic attacks, range from no change to 38 beats per minute.<sup>65-71</sup> In 1 study,<sup>69</sup> heart rate did not change disproportionately during 42% of recorded panic attacks. This demonstrates that panic attacks can occur without substantial cardiac changes. Similar to previous ambulatory monitor studies,<sup>68,69,71</sup> 74% of our patients with PD had an increase in heart rate during the time of the button press. Thus, 26% of the panic attacks occurred without cardiac changes. However, the GAD and control groups had similar heart rate increases, which ranged from no change to 12 beats per minute. Thus, heart rate increase seems to be associated with increased tension or anxiety irrespective of the presence of panic attacks or anxiety disorder and despite prominent cardiac symptoms accompanying panic attacks. However, without obtaining constant analog recordings we may have missed brief changes in heart rhythm.

#### RELATION BETWEEN SUBJECTIVE AND PHYSIOLOGIC DATA

As reported by other researchers,<sup>22,72</sup> patients with PD were more sensitive to body sensations on self-ratings. Despite greater sensitivity, patients with PD and GAD were less accurate than controls in their perception of bodily states and showed substantially more variability. As demonstrated elsewhere,<sup>15,73</sup> patients are accurate in the estimation of the direction of bodily changes but not in their estimation of the degree of change and differ in levels of attention and expectations, which modify their perceptions. The discrepancy between self-reports of physical changes during panic attacks and the lack of such changes may be explained by a sensitization of the patients to body changes during early panic attacks. Recurrent somatic experiences may than create "engrams" in the brain that

can induce bodily sensations with minimally altering peripheral physiologic function. Such centrally induced panic attacks have been demonstrated by Lenz et al<sup>74</sup> who found, during surgery for intractable pain in a patient with panic attacks, that the stimulation of an area in the thalamus evoked panic attacks without causing the physical changes that the patient described.

#### LIMITATIONS OF THE AMBULATORY MONITOR STUDY

Ambulatory monitors measure responses in real-life situations, and their data have greater external validity than those obtained in the laboratory. However, the number of parameters that can be recorded and the length of the recordings are limited by memory, battery power, and the potential for technical failures. Moreover, the type and severity of stressors is unpredictable. Verification of panic attacks is easier in the laboratory than during ambulatory recording. Despite these shortcomings, we obtained adequate information on physiologic states throughout a day and responses before and after indication of stress, anxiety, or panic. Further studies are needed to clarify the relationship between reported somatic manifestations and physiologic responses in patients who differ in diagnosis, severity of illness, and family history and to integrate the data into the framework of imaging studies.

Submitted for publication January 13, 2003; final revision received March 10, 2004; accepted March 16, 2004.

This study was supported by grant MH42579 from the National Institute of Mental Health, Bethesda, Md.

Correspondence: Rudolf Hoehn-Saric, MD, Department of Psychiatry, The Johns Hopkins Medical Institutions, 600 N Wolfe St, Meyer Bldg, Room 113, Baltimore, MD 21287-7113 (rhoehn@mail.jhmi.edu).

#### REFERENCES

1. Hoehn-Saric R, McLeod DR. Somatic manifestations of normal and pathological anxiety. In: Hoehn-Saric R, McLeod DR, eds. *Biology of Anxiety Disorders*. Washington, DC: American Psychiatric Press; 1993:177-222.
2. Ursin H, Murison RCC. Classification and description of stress. In: Brown GM, Koslow SH, Reichlin S, eds. *Neuroendocrinology and Psychiatric Disorder*. New York, NY: Raven Press; 1984:123-131.
3. Frankenhaeuser M. Psychoneuroendocrine approaches to the study of emotion as related to stress and coping. In: Howe HEJ, ed. *Nebraska Symposium on Motivation*. Lincoln: University of Nebraska Press; 1979:123-161.
4. Generalized anxiety disorder. In: Noyes RJ, Hoehn-Saric R. *The Anxiety Disorders*. New York, NY: Cambridge University Press; 1998:37-85.
5. Hoehn-Saric R, McLeod DR, Zimmerli WD. Somatic manifestations in women with generalized anxiety disorder. *Arch Gen Psychiatry*. 1989;46:1113-1119.
6. Kollai M, Kollai B. Cardiac vagal tone in generalised anxiety disorder. *Br J Psychiatry*. 1992;161:831-835.
7. Lyonfields JD, Borkovec TD, Thayer JF. Vagal tone in generalized anxiety disorder and the effects of aversive imagery and worrisome thinking. *Behav Ther*. 1995; 26:457-466.
8. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. *Biol Psychiatry*. 1996;39:255-266.
9. Stein MB, Asmundson GJ. Autonomic function in panic disorder: cardiorespiratory and plasma catecholamine responsiveness to multiple challenges of the autonomic nervous system. *Biol Psychiatry*. 1994;36:548-558.
10. Friedman BH, Thayer JF. Autonomic balance revisited: panic anxiety and heart rate variability. *J Psychosom Res*. 1998;44:133-151.
11. Friedman BH, Thayer JF. Anxiety and autonomic flexibility: a cardiovascular approach. *Biol Psychol*. 1998;49:303-323.
12. Yeragani VK, Balon R, Pohl R, Ramesh C, Glitz D, Weinberg P, Merlos B. Decreased R-R variance in panic disorder patients. *Acta Psychiatr Scand*. 1990;81: 554-559.



13. Klein E, Cnaani E, Harel T, Brown S, Ben Haim SA. Altered heart rate variability in panic disorder patients. *Biol Psychiatry*. 1995;37:18-24.
14. Wilhelm FH, Trabert W, Roth WT. Physiological instability in panic disorder and generalized anxiety disorder. *Biol Psychiatry*. 2001;49:596-605.
15. McLeod DR, Hoehn-Saric R. Perception of physiological changes in normal and pathological anxiety. In: Hoehn-Saric R, McLeod DR, eds. *Biology of Anxiety Disorders*. Washington, DC: American Psychiatric Press; 1993:223-243.
16. First MB, Spitzer RL, Gibbon M, Williams J. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press; 1997.
17. Spielberger CD, Gorsuch RL, Lushene RE. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, Calif: Consulting Psychologists Press; 1970.
18. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32:50-55.
19. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive Therapy of Depression*. New York, NY: Guilford Press; 1979.
20. Sheehan DV. *The Anxiety Disease*. New York, NY: Scribner; 1983.
21. Barsky AJ, Goodson JD, Lane RS, Cleary PD. The amplification of somatic symptoms. *Psychosom Med*. 1988;50:510-519.
22. Chambless DL, Caputo GC, Bright P, Gallagher R. Assessment of fear in agoraphobics: the Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire. *J Consult Clin Psychol*. 1984;52:1090-1097.
23. Hoehn-Saric R, McLeod DR, Zimmerli WD. Symptoms and treatment responses of generalized anxiety disorder patients with high versus low levels of cardiovascular complaints. *Am J Psychiatry*. 1989;146:854-859.
24. Thakor NV, Yang M, Amaresan M, Reiter E, Hoehn-Saric R, McLeod DR. Micro-computer-based ambulatory monitor for vital signs in anxiety disorders. *J Ambul Monit*. 1989;2:277-294.
25. Fowles DC, Christie MJ, Edelberg R. Publication recommendations for electrodermal measurements. *Psychophysiology*. 1981;18:232-239.
26. Jennrich RI, Schluchter MD. Unbalanced repeated-measures models with structured covariance matrices. *Biometrics*. 1986;42:805-820.
27. Jones RH, Boadi B. Unequal spaced longitudinal data with AR(1) serial correlation. *Biometrics*. 1991;47:161-175.
28. Willett JB, Sayer AG. Using covariance structure analysis to detect correlations and predictors of individual change over time. *Psychol Bull*. 1994;116:363-381.
29. Cohen J, Cohen P. *Applied Multiple Regression/Correlation Analysis for the Behavioral Science*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1975.
30. Anderson DJ, Noyes R, Crowe RR. A comparison of panic disorder and generalized anxiety disorder. *Am J Psychiatry*. 1984;141:572-575.
31. Hoehn-Saric R. Comparison of generalized anxiety disorder with panic disorder patients. *Psychopharmacol Bull*. 1982;18:104-108.
32. Logue MB, Thomas AM, Barbee JG, Hoehn-Saric R, Maddock RJ, Schwab J, Smith RD, Sullivan M, Beitman BD. Generalized anxiety disorder patients seek evaluation for cardiologic symptoms at the same frequency as patients with panic disorder. *J Psychiatr Res*. 1993;27:55-59.
33. McLeod DR, Foster GV, Hoehn-Saric R, Svikis DS, Hipsley PA. Family history of alcoholism in women with generalized anxiety disorder who have premenstrual syndrome: patient reports of premenstrual alcohol consumption and symptoms of anxiety. *Alcohol Clin Exp Res*. 1994;18:664-670.
34. McLeod DR, Hoehn-Saric R, Foster GV, Hipsley PA. The influence of premenstrual syndrome on ratings of anxiety in women with generalized anxiety disorder. *Acta Psychiatr Scand*. 1993;88:248-251.
35. Charney DS, Woods SW, Goodman WK, Heninger GR. Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. *Am J Psychiatry*. 1987;144:1030-1036.
36. Asmundson GJ, Stein MB. Resting cardiovascular measures in patients with panic disorder and social phobia and health control subjects: relationship to habitual exercise frequency. *Anxiety*. 1994;1:26-30.
37. Abelson JL, Weg JG, Nesse RM, Curtis GC. Persistent respiratory irregularity in patients with panic disorder. *Biol Psychiatry*. 2001;49:588-595.
38. Martinez JM, Papp LA, Coplan JD, Anderson DE, Mueller CM, Klein DF, Gorman JM. Ambulatory monitoring of respiration in anxiety. *Anxiety*. 1996;2:296-302.
39. Roth WT, Wilhelm FH, Trabert W. Autonomic instability during relaxation in panic disorder. *Psychiatry Res*. 1998;80:155-164.
40. Hoehn-Saric R, McLeod DR, Zimmerli WD. Psychophysiological response patterns in panic disorder. *Acta Psychiatr Scand*. 1991;83:4-11.
41. Hoehn-Saric R, McLeod DR, Hipsley P. Is hyperarousal essential to obsessive-compulsive disorder? diminished physiologic flexibility, but not hyperarousal, characterizes patients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1995;52:688-693.
42. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *Am J Cardiol*. 1995;75:882-885.
43. Cohen H, Kotler M, Matar A, Kaplan Z, Miodownik H, Cassuto Y. Power spectrum analysis of heart rate variability in posttraumatic stress disorder. *Biol Psychiatry*. 1997;41:627-629.
44. Thayer JF, Smith M, Rossy LA, Sollers JJ, Friedman BH. Heart period variability in depressive symptoms: gender differences. *Biol Psychiatry*. 1998;44:304-306.
45. Kirsch JR, Geer JH. Skin conductance and heart rate in women with premenstrual syndrome. *Psychosom Med*. 1988;50:175-182.
46. Ingjaldsson JT, Laberg JC, Thayer JF. Reduced heart rate variability in chronic alcohol abuse: relationship with negative mood, chronic thought suppression, and compulsive drinking. *Biol Psychiatry*. 2003;54:1427-1436.
47. Forsman L. Habitual catecholamine excretion and its relation to habitual distress. *Biol Psychol*. 1980;11:83-97.
48. Shapiro D, Crider A. Psychophysiological approaches in social psychology. In: Lindzey G, Aronson E, eds. *The Handbook of Social Psychology*. 2nd ed. Reading, Pa: Addison-Wesley Publishing Co; 1969:1-49.
49. Hubert W, Jong-Meyer R. Saliva cortisol responses to unpleasant film stimuli differ between high and low trait anxious subjects. *Neuropsychobiology*. 1992;25:115-120.
50. Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL, Mason JW. Low urinary cortisol excretion in patients with post-traumatic stress disorder. *J Nerv Ment Dis*. 1990;178:366-369.
51. Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, Giller EL. Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry*. 1995;152:982-986.
52. Inz J. *EEG Activity in Generalized Anxiety Disorder* [doctoral dissertation]. University Park, Pa: Penn State University; 1990.
53. Tecce JJ. Contingent negative variation (CNV) and psychological processes in man. *Psychol Bull*. 1972;77:73-108.
54. Kelly D. *Anxiety and Emotions*. Springfield, Ill: Charles C Thomas Publisher; 1980.
55. Kagan J, Reznick JS, Snidman N. Biological bases of childhood shyness. *Science*. 1988;240:167-171.
56. Burchfield SR. The stress response: a new perspective. *Psychosom Med*. 1979;41:661-672.
57. Yehuda R, Resnick H, Kahana B, Giller EL. Longlasting hormonal alterations to extreme stress in humans: normative or maladaptive? *Psychosom Med*. 1993;55:287-297.
58. Grillon C, Buchsbaum MS. EEG topography of response to visual stimuli in generalized anxiety disorder. *Electroencephalogr Clin Neurophysiol*. 1987;66:337-348.
59. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord*. 2000;61:201-216.
60. Asmundson GJ, Stein MB. Vagal attenuation in panic disorder: an assessment of parasympathetic nervous system function and subjective reactivity to respiratory manipulations. *Psychosom Med*. 1994;56:187-193.
61. Moser M, Lehofer M, Hoehn-Saric R, McLeod DR, Hildebrandt G, Steinbrenner B, Voica M, Liebermann P, Zapotoczky HG. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *J Affect Disord*. 1998;48:115-124.
62. Hoehn-Saric R, Schlund MW, Wong SHY. Effect of citalopram on worry and brain activation in patients with generalized anxiety disorder. *Psychol Res Neuroimag*. In press.
63. Bishop S, Duncan J, Brett M, Lawrence DA. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. *Nat Neurosci*. 2004;7:184-188.
64. Hoehn-Saric R, McLeod DR. Anxiety and arousal: physiological changes and their perception. *J Affect Disord*. 2000;61:217-224.
65. Lader MH, Mathews A. Physiological changes during spontaneous panic attacks. *J Psychosom Res*. 1970;14:377-382.
66. Balon R, Ortiz A, Pohl R, Yeragani VK. Heart rate and blood pressure during placebo-associated panic attacks. *Psychosom Med*. 1988;50:434-438.
67. Goetz RR, Klein DF, Gully R, Kahn J, Liebowitz MR, Fyer AJ, Gorman JM. Panic attacks during placebo procedures in the laboratory. *Arch Gen Psychiatry*. 1993;50:280-285.
68. Freedman RR, Ianni P, Etedgui E, Putezhath N. Ambulatory monitoring of panic disorder. *Arch Gen Psychiatry*. 1985;42:244-248.
69. Taylor CB, Sheikh J, Agras S, Roth WT, Margraf J, Ehlers A, Maddock RJ, Gosard D. Ambulatory heart rate changes in patients with panic attacks. *Am J Psychiatry*. 1986;143:478-482.
70. Woods SW, Charney DS, McPherson CA, Gradman AH, Heninger GR. Situational panic attacks: behavioral, physiologic, and biochemical characterization. *Arch Gen Psychiatry*. 1987;44:365-375.
71. Taylor CB, Sheikh J, Agras S, Roth WT, Margraf J, Ehlers A, Maddock RJ, Gosard D. Ambulatory heart rate changes in patients with panic attacks. *Am J Psychiatry*. 1986;143:478-482.
72. Clark DM, Salkovskis PM, Ost LG, Breitholtz E, Koehler KA, Westling BE, Jeavons A, Gelder M. Misinterpretation of body sensations in panic disorder. *J Consult Clin Psychol*. 1997;65:203-213.
73. McLeod DR, Hoehn-Saric R, Stefan RL. Somatic symptoms of anxiety: comparison of self-report and physiological measures. *Biol Psychiatry*. 1986;21:301-310.
74. Lenz FA, Gracely RH, Romanoski AJ, Hope EJ, Rowland LH, Daugherty PM. Stimulation in the human somatosensory thalamus can reproduce both the affective and sensory dimensions of previously experienced pain. *Nat Med*. 1995;1:910-913.