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Stress Test Reactivity in Panic Disorder

Walton T. Roth, MD; Jürgen Margraf, PhD; Anke Ehlers, PhD; C. Barr Taylor, MD; Richard J. Maddock, MD; Sylvia Davies; W. Stewart Agras, MD

- The psychological and physiological reactivity of 52 patients with panic disorder to mental arithmetic, cold pressor, and 5% carbon dioxide inhalation tests was compared with that of 26 age- and sex-matched normal subjects. In general, patients with panic disorder were neither more nor less reactive to these stressors than normal subjects. However, they were more anxious and much more likely to ask to stop carbon dioxide inhalation or to report panic attacks during this test. Patients who reported panic attacks (46%) had manifested greater anticipatory anxiety before the gas was delivered, accompanied with increased β-adrenergic cardiac tone. Thus, anticipatory anxiety can be an important factor in panic provocation. Physiological measures varied greatly in their sensitivity to phasic or tonic anxiety. Carbon dioxide stimulated large increases in respiratory minute volume, but these increases were no greater for patients than for normal subjects.

(Arch Gen Psychiatry. 1992;49:301-310)

Many studies have concluded that patients with panic disorder manifest greater subjective anxiety and more signs and symptoms of autonomic activation during challenges with anxiety-inducing agents or procedures than do control subjects. Sometimes, but not always, greater reactivity is observed, in the sense of greater increases from before-challenge to during-challenge levels (see Table 1 in Aronson et al for a comparison of lactate studies in this light). Emphasis has been on which challenges are most effective in inducing panic attacks, in hope of finding clues to the nature of the biological mechanisms of spontaneous panic attacks. For example, lactate infusion and carbon dioxide inhalation have seemed more potent than hyperventilation.

To understand reactivity to challenges, it is useful to examine the specificity of these effects by administering more than one challenge to the same subject, to measure anticipatory reactions, and to use multiple response measures. Eysenck has characterized "neurotics" as being generally more reactive autonomically than nonneurotics. Our anxious patients more often than normal subjects endorse questionnaire items attributing to themselves a general emotional or visceral hyperreactivity (W.T.R., unpublished results, 1990). Anticipatory reactions are important since it is plausible that patients with panic disorder would be more fearful in laboratory situations where panic induction is on the agenda. An aversive challenge might additionally raise anxiety levels above their threshold of tolerance and lead them to report panic. Anticipatory anxiety reflects certain expectations, and it has been demonstrated in several studies that expectations can alter reactions to anxiety provocations. Multiple response measures are necessary to index an emotional response such as anxiety or panic. Ideally, introspective, behavioral, and biological measures should all be considered. No single biological measure can be assumed to be representative, so multiple ones must be evaluated (eg, Myrtek).

This study compared the effects of three stressors—mental arithmetic, cold pressor, and CO₂ inhalation—in patients with panic disorder and matched normal controls. The first two, one producing stress by cognitive demand and the other by pain, are stressors that have not been proposed as having any special panic-inducing properties in patients with panic disorder; cold pressor, in fact, has been reported to produce the same blood pressure and prolactin responses in patients with panic disorder and normal subjects. However, they were included to control for the possibility that patients with panic disorder are more reactive to stressors in general. Carbon dioxide inhalation, on the other hand, has been postulated to trigger specific panic mechanisms. The design of the study allowed us to measure baseline levels, reactivity (ie, change from prestress to stress levels), and recovery of a number of cardiovascular and electrodermal variables associated with autonomic activation, and to compare them with subjective reports of moods and symptoms and with behavior. We also assessed ventilatory response to CO₂, since that has been reported to differ between patients with panic disorder and normal subjects. Special care was taken to exclude patients who were surreptitiously taking anxiolytic drugs.

Our cardiovascular variables included respiratory sinus arrhythmia, an index of parasympathetic cardiac tone, pulse transit time, an index of β-adrenergic cardiac tone,
and T-wave amplitude, a less specific measure of β-adrenergic cardiac tone. 17 These variables facilitate the interpretation of heart rate change, which results from changes in the balance between parasympathetic and sympathetic influences on the sinoatrial node.

Herein we report on 86 patients with panic disorder and 34 normal subjects. Our principal questions were these: (1) Do patients show higher prestress levels, greater stress reactivity, or slower recovery of measures of anxiety and autonomic activation? We already had demonstrated that patients with panic disorder do not react more strongly to innocuous novel stimuli, 18 although they habituate more slowly to aversive noise bursts. 19 (2) Are results similar for a variety of stressors, or does CO₂ have a special effect on patients with panic disorder? (3) Which autonomic variables are most sensitive to stressors and to group differences? Preliminary publications briefly presented anxiety, heart rate, and blood pressure data from the first 16 patients and 18 normal subjects 20 and described cognitions associated with anxiety in the first 20 patients and 10 normal subjects. 21

SUBJECTS AND METHODS

Subjects

Eighty-six patients with panic disorder were recruited through the media for a study comparing the effects of alprazolam, imipramine hydrochloride, and placebo 22 and participated in the testing protocol described below. As determined by the Structured Clinical Interview for DSM-III: Upjohn Version, 23 all met the panic attack criteria of DSM-III panic disorder, although some qualified for a DSM-III diagnosis of agoraphobia with panic attacks because of their extensive avoidance. Additionally, patients had to have had at least one attack in each of the 3 years before entering the study. Any major depressive episodes in the present or past needed to follow and not precede the panic attacks. Patients had to be in good health as determined by medical history, physical examination, electrocardiography, and blood and urine tests. They were told that they must stop taking psychoactive drugs 2 weeks before testing, and blood was drawn and assayed for diazepam, desmethyldiazepam, alprazolam, imipramine, and desmethylinimipramine at the laboratory session. Seventeen patients were excluded because of detectable levels of these compounds. In addition, six were excluded because of self-reported use of drugs (prescription, over-the-counter, or "recreational") during the previous 4 days that might have influenced our measures. Patients were not dropped for using estrogens postmenopausally or contraceptive pills. One patient, a marathon runner, was excluded because of possible effects of extreme physical conditioning on physiological variables. Also excluded were two patients who at the time of testing refused to begin the CO₂ inhalation test. Of the remaining pool of 86 subjects, 52 were chosen without regard to their test results who could be age and sex matched with our normal group. The final patient group consisted of 14 men (average age, 34.4 years) and 38 women (average age, 34.4 years). Fifteen of the patients had no agoraphobic avoidance, 29 had limited avoidance, and eight had agoraphobia with panic attacks.

Normal subjects were recruited by newspaper advertisement and screened over the telephone and in structured interviews. They were self-described as "nonanxious" and were free of a history of psychiatric problems as determined by the Structured Clinical Interview for DSM-III: Upjohn Version and a structured interview based on the Schedule for Affective Disorders and Schizophrenia—Lifetime version. 24 Anyone with significant health problems was rejected. In later phases of normal recruiting, we excluded potential subjects who engaged in regular, strenuous exercise to reduce the possibility that training effects would be confused with reduced anxiety-related cardiovascular activation. Thirty-four normal subjects passed this screening and participated in the testing protocol. Five were later excluded because of self-reported drug use before testing, and three because they could not be matched with patients, giving a final group of 26. It consisted of seven men (average age, 35.7 years) and 19 women (average age, 34.1 years). Education level was roughly equal for patients and normal subjects (average, 14.2 years for patients and 16.0 years for normal subjects).

Procedure

Testing took place in a sound-attenuated chamber where subjects could not see laboratory personnel but could communicate with them at any time. Four test paradigms were administered: a 15-minute baseline, cold pressor (ice water test), mental arithmetic, and CO₂ inhalation. Written instructions for each were read by the subject just before the first period of that test. Subjects were told initially that they could ask that a test be discontinued at any time, but this was not mentioned again to discourage their doing so. During testing they were treated as if they were expected to complete all tests, and were encouraged to continue if they expressed hesitation. The beginning and ending of each test period was announced by the experimenter through an intercom.

The baseline paradigm required subjects simply to sit with their eyes open for 15 minutes. The cold pressor test consisted of a 4-minute anticipation period, 1 minute during which the subject's dominant foot was immersed in ice water (4°C), and 7 minutes of recovery. The mental arithmetic test consisted of a 3-minute 45-second anticipation period, a 5-minute 15-second period of spoken serial subtractions of 13 from 7683, and a 7-minute recovery period. For the CO₂ inhalation test, subjects wore a continuous positive-pressure gas mask. For the first 15-minute anticipation period, they breathed compressed room air, which was switched secretly in an adjacent room to 5.5% CO₂ in room air for 20 minutes. Then the gas was switched back to room air for a 15-minute recovery period. Continuous monitoring with a capnometer ensured that air inhaled during the CO₂ period had a CO₂ concentration above 5%. Although subjects were "blind" to when CO₂ began, they were told when it was stopped. The CO₂ seemed to have a different smell than room air, so to increase the subjects' uncertainty about when they were receiving CO₂, the experimenter switched from air to CO₂ just long enough for one breath at minutes 4 and 9, and from CO₂ to air at minutes 19, 24, and 29. The baseline paradigm was always first, and the CO₂ inhalation always last, since we thought that it might cause subjects to terminate the session. The order of cold pressor and mental arithmetic was balanced across subjects.

Physiological Recording

At the beginning of the session, a pair of silver-silver chloride electrodes, 0.8 cm² in area, was placed on the thenar and hypothenar eminences of the nondominant hand for recording skin conductance. The skin conductance transducer applied a constant 0.5 V across the electrodes. The electrode medium was a mixture of creamy ointment and physiological saline as recommended by Fowles et al. 25 An electrocardiogram was recorded from electrodes over the left 10th rib at the anterior axillary line and the right mastoid. A photoreflective skin blood-flow transducer was put on the nondominant thumb (123-04, Coulbourn Instruments, Lehigh Valley, Pa.). For 41 of the patients and 16 of the controls, an impedance registration of changes in blood volume during the cardiac cycle was made from electrodes on the dominant forearm, one measurement electrode placed on the dorsum of the forearm slightly proximal to the wrist and the other slightly distal to the elbow. Two elastic belts were placed over the rib cage and abdomen, respectively, and were connected to a device that measures chest movement during respiration by changes in self-inductance (Respiract Corporation, Ardsley, NY). This device was calibrated for respiratory volume by having subjects breathe into a spirometer. Body movement in the chair was monitored piezoelectrically with a phonograph cartridge mounted in the seat.

Systolic and diastolic blood pressure were measured oscillometrically by an automatic device (Accutorr 2, Datascope Corp., Paramus, NJ). The first blood pressure measurement was 302
seconds after the start of each paradigm and then every 4.5 minutes during the baseline, every 2 minutes during the cold pressor test (including a measurement at the end of immersion) and mental arithmetic test, and every 2.5 minutes during CO2 inhalation. Inflation of the cuff, which was placed on the nondominant arm, caused large changes in finger blood flow registered by the device described above.

**Psychological Assessment**

A number of self-rating instruments were employed. Subjects filled out an Anxiety Rating Scale26 form right after each deflation of the blood pressure cuff. Subjects rated themselves on “anxiety” and “excitement,” each on a scale from 0 (labeled “none”) to 10 (labeled “extreme”). The latter scale was included because physiological activation can correspond to excitement as well as anxiety. After about one third of the subjects had been tested, we started giving a symptom checklist of 20 yes/no items, of which 15 were panic symptoms (all of the DSM-III list) and five were control symptoms (e.g., feeling itchy, burning ears) during the initial room-air period of the CO2 stressor, during CO2 inhalation, and during the recovery period. After CO2 subjects completed their CO2 experience with their usual panic attacks (patients) or the most extreme anxiety ever experienced (normal subjects) on an 11-point scale (from −5, indicating very dissimilar, to +5, indicating very similar).

**Data Reduction and Statistical Analysis**

Continuously recorded physiological data were digitized and stored on tape for off-line analysis. Sampling rates were 200 Hz for the electrocardiographic, plethysmographic, and body movement channels and 20 Hz for skin conductance and respiration. Cardiovascular variables included heart rate calculated from R-R intervals, T-wave amplitude, finger pulse amplitude calculated as the difference between maximum and minimum levels during each cardiac cycle, and pulse transit times calculated from R waves to maxima in the forearm impedance channel and in the finger blood-flow channel. Nonspecific skin conductance fluctuations were defined as an increase in skin conductance level (SCL) of 0.05 microsiemens occurring within 3.5 seconds after a change in SCL slope of at least 0.01 microsiemens per second from a positive or negative value. Respiratory rate and minute volume were calculated from the respiratory volume curves using a computer algorithm. Respiratory sinus arrhythmia was quantified by measuring the mean difference in R-R interval between inspiratory and expiratory phases of the breathing cycle.27 Body movement was quantified as the integral of the absolute values of the transducer output around its mean.

Statistical analyses were based on mean values of purely cardiovascular variables over 10-second epochs, and mean values of other variables over 30-second epochs. Data were edited to exclude sensor and motion artifacts and periods when the blood pressure cuff was inflated. Repeated-measures univariate analysis of variance (ANOVA) with statistical significance levels adjusted according to the Greenhouse-Geisser correction was a principal statistical method. We did not use multivariate ANOVA since many of the variables we wanted to analyze were expected to be affected only by specific factors. Subanalyses of variance and post hoc comparisons of means were applied selectively to locate the source of interactions and explore questions of interest.

Data from the baseline paradigm were averaged into three 5-minute epochs and analyzed in a two-way ANOVA with group as one factor and time (epochs 1 through 3) as a second, repeated-measures factor. Data from the stress paradigms were averaged into prestress (anticipatory), stress, and poststress (recovery) periods for each stressor, and a three-way repeated-measures ANOVA was performed. Factors were stressor (cold pressor, arithmetic, CO2), time (before, during, after stress), and group (patients, normal subjects). Stressor and time but not group were repeated measures. Following the recommendations of Venables and Christie,28 SCL was log-transformed before statistical analysis.

### Table 1.—Results of Stress Tests

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Normal Subjects</th>
<th>P*&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Request to Stop Stress Test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of Subjects</td>
<td>52</td>
<td>26</td>
<td>. . .</td>
</tr>
<tr>
<td>Test:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold pressor</td>
<td>1</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>CO2</td>
<td>16</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Reasons Given for Stopping CO2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>16</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Principal reason:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panic attacks</td>
<td>14</td>
<td>1</td>
<td>.001</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Panic Attacks During CO2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>24</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>Evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Report of attack:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High rating of similarity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+4 or +5) to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>natural attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or extreme anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(normal subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety-increase</td>
<td>24</td>
<td>2</td>
<td>.01</td>
</tr>
<tr>
<td>&gt;=4</td>
<td>21</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;=6</td>
<td>7</td>
<td>6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P based on χ² statistic. NS indicates not significant.

In one analysis, we grouped subjects into patient panicers, patient nonpanicers, and normal subjects (none of whom reported panic) according to diagnosis and report of experiencing panic during CO2. Panic was either spontaneously reported during that stressor, was recorded on a “panic diary” that patients kept on testing days, or was reported on experimenter inquiry. In contrast to these broad subjective panic criteria, in another, overlapping analysis (overlapping because most “stoppers” were panicers), we grouped subjects according to a strict behavioral criterion: asking to stop the CO2 stressor. In stoppers, the stress period contained fewer data than in “completers” and was biased in time toward earlier measurements. However, some data were available for every subject in each epoch of each stressor. Since there were not enough normal stoppers to form a separate group, the categories under group were patient stoppers, patient completers, and normal completers.

In addition, a heart rate index that Gorman et al29 found able to distinguish “early” panicers and controls during lactate infusion was applied to heart rate during CO2 inhalation in our subjects. The index is the percentage increase of maximum heart rate during CO2 administration over the heart rate 3 minutes before the maximum, using heart rate analysis epochs of 30 seconds.

**RESULTS**

**Patients vs Normal Subjects**

During the baseline paradigm, patients had higher subjective anxiety (P<.001) and higher heart rates (P<.05). The ANOVAs of the stress paradigms showed that each variable was sensitive to the stressors since each showed highly significant time effects (all P<.001). Group membership influenced subjective anxiety, heart rate, systolic and diastolic blood pressure, pulse transit time, nonspecific skin conductance fluctuations, and respiratory rate as indicated by significant main group effects or group interactions. Details about these effects and follow-up statistical analysis of the interactions are not presented because the heterogeneity of patient reactions to CO2 documented in Table 1 ne-

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Stress Test—Roth et al 303
Means of patient nonpanickers (solid squares), patient panickers (solid triangles), and normal subjects (open squares) for baseline and stressors. The baseline is divided into consecutive 5-minute epochs (1, 2, and 3), and the stressors into prestressor (1), stressor (2), and poststressor (3) periods.

It was noted that patients be separated into subgroups for analysis to be meaningful.

Patients requested stopping CO₂ more than other stressors ($\chi^2, P<.001$), which was not the case for normal subjects. A direct comparison of the stopping rate of patients and normal subjects during CO₂ just failed to reach significance ($\chi^2, P<.07$). The principal reason patients gave for stopping CO₂ in almost all cases was that it elicited a panic attack, although a few gave headache as a secondary reason. Two patients claimed headache as the primary reason for stopping and denied having had panic attacks. As Table 1 shows, about half of the patients but none of the normal subjects reported panic attacks during CO₂. About 40% of the attacks reported by patients as occurring during CO₂ did not result in requests to stop. Although attacks reported by patients were rated as similar to natural attacks, large increases in subjective anxiety during CO₂ were not more common proportionately among patients than among normal subjects.

**Patient Panickers vs Patient Nonpanickers vs Normal Subjects**

We grouped subjects into the 24 patients who reported panic attacks during CO₂ (four men and 20 women), the 28 patients who did not (10 men and 18 women), and the 26 normal subjects (seven men and 19 women). The proportion of men was somewhat lower among panickers compared with nonpanickers, but the groups did not differ significantly ($\chi^2, P=.30$). Because of
Table 2.—Overall Stress Test Significance Levels for Patient Nonpanickers, Patient Panickers, and Normal Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>S</th>
<th>T</th>
<th>G</th>
<th>S × T</th>
<th>S × G</th>
<th>T × G</th>
<th>S × T × G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anxiety</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.05</td>
<td>.05</td>
<td>.01</td>
</tr>
<tr>
<td>Excitement</td>
<td>NS</td>
<td>.001</td>
<td>.05</td>
<td></td>
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<tr>
<td>Cardiovascular</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>.05</td>
<td>.001</td>
<td>.05</td>
<td>.001</td>
<td>.05</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Systolic BP</td>
<td>.001</td>
<td>.001</td>
<td>.05</td>
<td>NS</td>
<td>.01</td>
<td>.01</td>
<td>.05</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>.001</td>
<td>.001</td>
<td>NS</td>
<td>.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RSA</td>
<td>.001</td>
<td>.001</td>
<td>NS</td>
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<td>FPA</td>
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<td>.001</td>
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<td>.001</td>
<td>.05</td>
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<td>NS</td>
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<td>TWA</td>
<td>.001</td>
<td>.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>Electrodermal</td>
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<tr>
<td>SCL</td>
<td>.001</td>
<td>.001</td>
<td>NS</td>
<td>.001</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>NSF</td>
<td>.01</td>
<td>.001</td>
<td>NS</td>
<td>.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>Respiratory</td>
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<tr>
<td>Rate</td>
<td>.01</td>
<td>.001</td>
<td>NS</td>
<td>.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Minute volume</td>
<td>.001</td>
<td>.001</td>
<td>NS</td>
<td>.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Movement</td>
<td>.001</td>
<td>.001</td>
<td>NS</td>
<td>.001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*S indicates stressor; T, time; G, group; NS, not significant; BP, blood pressure; RSA, respiratory sinus rhythm; PTT, pulse transit time; FPA, finger pulse amplitude; TWA, T-wave amplitude; SCL, skin conductance level; and NSF, nonspecific skin conductance fluctuations. All values are P < (eg, P < .001).

missing data, not every subject is represented in every one of these analyses. The Figure gives the means of each group under each experimental condition.

Baseline Paradigm.—Group effects were significant for subjective anxiety (P < .001) and diastolic blood pressure (P < .05). Post hoc tests showed that each of the anxiety differences was significant: patients who would go on to panic (panickers) had greater anxiety than patients who would not panic (nonpanickers; P < .01), and nonpanickers were more anxious than normal subjects (P < .01). Diastolic blood pressure was greater for nonpanicking patients than for normal subjects (P < .05).

Stress Paradigms.—Table 2 summarizes the ANOVAs of the stress tests. Group membership affected about two thirds of the variables, as witnessed by significant main group effects or group interactions. Group did not affect respiratory sinus arrhythmia, T-wave amplitude, SCL, respiratory rate, or minute volume.

Subanalyses of variance and comparisons of means were applied systematically to elucidate statistical effects involving group. For example, all variables showing a stressor × time × group interaction were subjected to ANOVA for each stressor alone. If a group × time interaction was significant, group effects were tested separately at the three time points (before, during, and after). If a group effect was present at a given time point, groups were compared with each other using the Tukey Studentized Range statistic corrected for inequality of sample size. If a main group effect was significant but the corresponding group × time interaction was not, group comparisons were made for all time points combined. Reference to the Figure helps to visualize the patterns described below. (Note that the order of paradigms portrayed in these and other figures is correct only insofar as the baseline paradigm was always first and the CO2 paradigm always last. The order of cold pressor and mental arithmetic was balanced across subjects.)

Four variables showed stressor × group interactions without stressor × time × group interactions: excitement, heart rate, diastolic blood pressure, and finger pulse amplitude. This pattern means that groups reacted differently to individual stress paradigms, but that these were not merely differences in reactions to the stressor itself. For excitement, a group effect was present only for CO2 (P < .01), patient panickers being more excited than patient nonpanickers (P < .05) or normal subjects (P < .01) throughout the CO2 paradigm. For heart rate, group effects were present for both cold pressor (P < .05) and CO2 (P < .01). Patient panickers had heart rates higher than those of normal subjects throughout both paradigms (P < .01) and higher than those of patient non-panickers for CO2 (P < .05). The locus of the effects for diastolic blood pressure and finger pulse amplitude could not be determined since there was no significant group effect for any stressor.

Four variables showed stressor × time × group interactions: subjective anxiety, systolic blood pressure, pulse transit time, and nonspecific skin conductance fluctuations. Such interactions mean that groups reacted to stressors differently, and that the differences were not the same before, during, and after a stressor. For cold pressor, anxiety showed a group × time × interaction (P < .001) with significant group effects before, during, and after the stressor. At all time points, patient panickers were more anxious than normal subjects (all P < .01), and before the stressor, patient panickers were more anxious than normal subjects as well (P < .05). For mental arithmetic, only anxiety showed a group × time interaction (P < .01). Before the stressor, patient panickers were more anxious than either patient nonpanickers (P < .05) or normal subjects (P < .01). After the stressor, patient panickers were again more anxious than normal subjects (P < .01).

The statistical analysis for the CO2 paradigm is presented in Table 3. Patient panickers reported significantly more anxiety than patient nonpanickers, who reported significantly more anxiety than normal subjects. This pattern was present before, during, and after the stressor, as indicated by the lack of a group × time interaction. For pulse transit time and systolic blood pressure, the pattern was more complicated: for pulse transit time, there was a group × time interaction because the decrease during stress was less in normal subjects than in patient groups; for systolic blood pressure, the group × time interaction must have been due to larger increases during CO2 for patient panickers than for patient nonpanickers, but subanalyses of variance were not significant at the different time points.

In the analyses above, greater patient reactivity to stressors could only be present in variables with stressor × time × group effects, since no variables showed time × group effects without stressor × time × group effects. For cold pressor and mental arithmetic, the only candidate for greater reactivity is subjective anxiety since it alone showed time × group effects in the follow-up analysis. However, in neither case did contrasts of means suggest that patients were more anxious than normal subjects during the stressor alone, as might be the case if patients were more reactive. For CO2, pulse transit time does follow this pattern, but examination of the means in the Figure (left) suggests it is probably an artifact of greater variance before the stressor than during it.

A different, less general but more easily interpretable ap-
Table 3.—Significance Levels for CO₂*

<table>
<thead>
<tr>
<th>Variable</th>
<th>G(group)</th>
<th>T(time)</th>
<th>GT</th>
<th>Tn</th>
<th>PN/PP</th>
<th>PN/N</th>
<th>PP/N</th>
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</thead>
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<tr>
<td>Anxiety</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NS</td>
<td>. . .</td>
<td>&lt;.01</td>
<td>&lt;.05</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>NS</td>
<td>&lt;.001</td>
<td>.01</td>
<td>T1:NS</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2:NS</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T3:NS</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>PTT</td>
<td>NS</td>
<td>&lt;.001</td>
<td>.01</td>
<td>T1:NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.05</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td>T2:&lt;.05</td>
<td>NS</td>
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<td></td>
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</tr>
<tr>
<td>NSF</td>
<td>NS</td>
<td>&lt;.001</td>
<td>.01</td>
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</tbody>
</table>

*BP indicates blood pressure; PTT, pulse transit time; NSF, nonspecific skin conductance fluctuations; PN, patient nonpanickers; PP, patient panickers; N, normal subjects; Tn, time effect for before (T1), during (T2), or after (T3) CO₂ inhalation. The G(group), T(time), and GT columns give the results of the analysis of variance. In cases where Group or GT effects were significant, the last three columns give comparisons of group means using Tukey's Studentized Range test corrected for inequality of sample size. In cases of GT effects, comparisons of group means were calculated only at time points where group effects were significant.

approach to testing for differences in reactivity and recovery was undertaken to supplement the ANOVA design used above. The difference between stressor and prestressor values (time 2 – time 1) was calculated for each subject as a measure of reactivity, and the difference between poststressor and prestressor values (time 3 – time 1) was calculated as a measure of recovery, and both measures were submitted to ANOVA. The only variables showing group or stressor × group effects for time 2 – time 1 were subjective anxiety (stressor × group; P < .01) and systolic blood pressure (group; P < .01). In the case of anxiety, patient panickers reacted to cold pressor and mental arithmetic less than normal subjects (both P < .01), and in the case of systolic blood pressure, patient nonpanickers reacted less than either of the other groups. Anxiety reactivity to CO₂ did not differ between groups. The only variables showing group or stressor × group effects for time 3 – time 1 were pulse transit time (stressor × group; P < .001) and SCL (stressor × group; P < .05). In the case of pulse transit time, patient panickers recovered faster from CO₂ than either patient nonpanickers or normal subjects (both P < .05), and in the case of SCL, patient nonpanickers recovered faster from CO₂ than normal subjects (P < .05).

Comparison of measures between the baseline paradigm and the prestressor period of the CO₂ paradigm tells us if any prestressor group differences in this paradigm were already present during the baseline or if they arose when subjects began to breathe room air through the mask. For subjective anxiety, the absence of a group × paradigm (baseline vs CO₂ prestressor) interaction in the face of a main group effect (P < .001) indicated that the groups differed in anxiety level approximately as much during baseline as just before CO₂. On the other hand, group × paradigm interactions were significant for subjective excitement (P < .05), heart rate (P < .001), systolic blood pressure (P < .05), pulse transit time (P < .05), T-wave amplitude (P < .05), and nonspecific skin conductance fluctuations (P < .05), which corresponded to a pattern of patients deviating more from normal subjects before CO₂ than during baseline. Before CO₂ but not during baseline, excitement, heart rate, and nonspecific skin conductance fluctuations were greater in both patient groups than in normal subjects (P < .05 or less). Before CO₂ but not during baseline, patient panickers had shorter pulse transit times than either other group (P < .05 or less).

For CO₂ inhalation, the number of symptom checklist panic symptoms showed a greater rise (group × time; P < .03) in patient panickers (from a mean of 3.6 during air inhalation to 8.6 during CO₂ inhalation) than in patient nonpanickers (from 2.2 to 4.5). Control symptoms did not show these effects.

Patient Stoppers vs Patients Completers vs Normal Completers

We also grouped patients according to the behavioral criterion of stopping or completing the CO₂ paradigm into 36 patient completers (10 men and 26 women), 16 patient stoppers (four men and 12 women), and 23 normal completers (six men and 17 women). The proportions of men were almost equal in these three categories (χ² = .98). The three normal stoppers were too few to compose a separate category, so they were excluded from this analysis. Patient stoppers included two who claimed headache as a reason for stopping, and patient completers included 10 who reported panic attacks, which might dilute the differences described above. However, differences turned out to be greater, not smaller, with this grouping. Because of the substantial overlap between this grouping and the previous one and the similarity of results between them, only a detail of the statistical analysis will be presented herein (we will provide the complete analysis on request).

For the CO₂ paradigm, group × time interactions were significant for pulse transit time (P < .05) and respiratory sinus arrhythmia (P < .01). Post hoc tests showed that during CO₂ inhalation, pulse transit time was less for patient stoppers than for normal completers (P < .05), while respiratory sinus arrhythmia was less for patient completers than for normal completers (P < .01). Thus, during CO₂ inhalation, patient stoppers had the highest β-adrenergic cardiac tone, while patient completers had the lowest vagal cardiac tone. In view of their near-equal heart rates, different mechanisms of cardiac stress regulation are suggested.

Heart Rate Index

The heart rate index, using the 10-beat per minute cutoff found optimal by Gorman et al34 for detecting lactate-induced panic attacks, classified 33% of the patient panickers, 10% of the patient nonpanickers, and 31% of the normal subjects as having had panic attacks during CO₂ (χ², not significant). Applying it to the second grouping, it classified 50% of the patient stoppers, 7% of the patient continuers, and 29% of the controls as having had a panic attack (χ², P < .05). The index was less discriminatory when heart rates earlier or later than 3 minutes before the maximum were used.

COMMENT

Subjective anxiety and heart rate were tonically higher in patients during the baseline paradigm and all stress paradigms, suggesting that the laboratory situation, possibly because of a generalized anticipation of challenges or more specifically anticipation of the presumably panic-inducing CO₂, caused the patients to be anxious from the moment they stepped inside the laboratory door or even in the hours or days before making that step. Signs of tonic physiological activation in laboratory settings beginning before any stressors are given have been reported in other samples of patients with panic disorder.2,18,30 However, evidence from an ambulatory monitoring study32 suggests that patients do not have higher heart rates than normal subjects during nonpanic periods outside the laboratory, indicating either that physiological
activation occurs under the psychological influence of imminent laboratory testing or alternatively that physiological adaptation, such as β-adrenergic down-regulation, lowers heart rate to normal levels in the average out-of-laboratory situation even when psychic anxiety persists.

Patients with panic disorder were not generally more physiologically reactive to specific laboratory stressors than were normal subjects, although the physiological measures were sensitive to the stressors. Differences in reactivity or recovery would be manifested in time × group or stressor × time × group interactions for the measures taken before, during, and after stressors, or in group or stressor × group effects for stressor-prestressor differences (reactivity) or poststressor-prestressor differences (recovery). Statistical analysis did not support reactivity differences but did suggest that pulse transit time recovered faster from CO₂ in patient panicers than in other groups and that SCL recovered faster from CO₂ in patient nonpanicers than in normal subjects. Note that the validity of our inferences about reactivity rests on our subjective and physiological scales being essentially linear, i.e., that an increase in a given number of units from a higher initial value does not represent a smaller increase in underlying anxiety or activation than an equal scale increase from a lower initial value. Linearity is difficult to prove, but in favor of this assumption for at least heart rate and blood pressure is the fact that these variables never approached physiological floors or ceilings in our experiment.

Although Eysenck's view characterizing neurotics as generally more reactive autonometrically than nonneurotics is contradicted by our reactivity measures to specific stressors, higher baseline and prestressor values in patients may be consistent with a greater reactivity to the laboratory in general or to the threat of stressors. Furthermore, in this experiment, psychological reactivity to the CO₂ stressor was clearly different in patients than in normal subjects in that about half of the patients but none of the normal subjects reported that CO₂ produced a panic attack. This rate of panicizing corresponds exactly to the rate expected from the literature, according to the extensive review of Sanderson and Wetzler. Whether these attacks were really the same as natural panic attacks, however, is a matter of interpretation. Large increases in reported anxiety were equally frequent in patients and normal subjects, although the latter did not label their experience as panic and rarely asked to stop. Having had panic attacks made this labeling natural for patients, especially if CO₂ elicited bodily sensations in common with previous attacks. Furthermore, the demand characteristics of the situation may have biased patients toward reporting panic attacks: first, patient subjects may well have believed that the experimenter expected them to have an attack during the most unusual, impressive, and longest stressor in our experiment; second, reporting a panic attack justified requesting us to stop the unpleasant CO₂ stressor.

It may be fallacious to assume that natural panic attacks are a single entity, even within an individual subject. Ronald Ley, PhD (written communication, October 1990), has suggested that there are three types: classic, cognitive, and anticipatory. The classic type is accompanied by sudden large increases in autonomic activation (see, for example, Lader and Mathews and Margraf et al), sometimes beginning in a period of relative relaxation. Cognitive attacks are triggered by fearful thoughts that may not be accompanied by much autonomic reaction. Anticipatory attacks are reported when anticipatory anxiety rises above a threshold of tolerance. Autonomic activation increases to a certain extent but not abruptly or dramatically. Perhaps it is predominantly the last type that CO₂ elicited in our patient panicers.

In any case, the most parsimonious explanation for certain of our patients reporting panic attacks during CO₂ is that they started the session with greater fear and that CO₂ raised this fear further, to a level difficult for anyone to tolerate or at least to a level that patients with panic disorder cannot tolerate. Patient panicers reported significantly higher anxiety levels than other patients and normal subjects during a baseline paradigm more than 30 minutes before CO₂ was given. Of the physiological variables, pulse transit time followed a pattern of increased differentiation in the pre-CO₂ period between patient panicers and other patients; heart rate rises from baseline to pre-CO₂ were greater for patients than for normal subjects but did not differentiate patient panicers from other patients. Note that pre-CO₂ increases cannot be attributed to the influences of the two stress tests that went before CO₂, since reactivity to them was not greater, nor recovery slower, in the patient groups that showed the increases. In fact, panicers reacted with smaller anxiety increases to cold pressor and to mental arithmetic than did other groups. Thus, anxiety reactivity among the groups was the same to CO₂ but different to the other stressors.

Differences in expectation, which have been demonstrated to be able to alter reactions to anxiety provocations, may have caused the differences in anticipatory anxiety levels and physiological activation we observed, although we did not directly test this by asking subjects what they expected. Biological factors may also have played an important role: individual differences in anticipatory anxiety undoubtedly have biological as well as psychological roots. A rapid escalation of anxiety may occur for biological reasons when a biologically set threshold is exceeded. Furthermore, interactions between psychological and biological processes may occur. For example, the fearful expectation of having a panic attack might raise anxiety to a point where a biological panic process is triggered, or conversely, biological susceptibility to anticipatory anxiety might raise anxiety to a point where catastrophic thinking supervenes.

Whether in every study baseline pre-CO₂ anxiety levels can explain the differential panic rates between patients and normal subjects, or why some patients panic while others do not, is less certain. By manipulating expectation, perhaps by increasing apparent controllability, baseline anxiety levels might be made more equal between patients and controls, although it is implausible that people who have had panic attacks can be made to believe that they are not to be feared when inhaling a gas administered by anxiety researchers as people who never have had attacks. For this reason, it is not surprising that baseline anxiety differences between patients and normal subjects before CO₂ inhalation have been observed by other investigators. However, the baseline differences between panicking and nonpanicking patients reported herein were not observed by Woods et al or Gorman et al. In the Woods et al study, anxiety ratings might have separated future panicers and nonpanicers better when the administration of CO₂ was more immi-
nent: the only pre-CO₂ baseline was the mean of values 15 and 30 minutes before testing in the context of a 4.5-hour session. However, in the Gorman et al study, a baseline apparently was taken only a few minutes before CO₂ administration. Perhaps their 17-item anxiety scale, which included the gamut of possible somatic anxiety symptoms, was less sensitive to the psychic fear component that distinguished our patient groups.

Our results contradict any simple theory that patients with panic disorder have an abnormal biological reaction to CO₂ manifested by greater proportional increases in respiratory minute volume to CO₂ levels in the inspired air. Our panickers actually had nonsignificantly smaller increases to CO₂, contrary to the results of some but consistent with those of others. Comparisons with previous studies must be made with caution, however, because of the diversity of assessment methods. Gorman et al. and Papp et al. introduced 5% CO₂ into a canopy over the subject's head. In this Gorman et al study, panicking patients had an exaggerated increase in respiratory minute volume to the first 2.5 minutes of CO₂ compared with nonpanickers and controls, but after 3 minutes group differences were no longer significant. Papp et al. found changes in the ratio of minute volume to arterial PCO₂ over 10 minutes of inhalation to be equal for a mixed sex sample of patients and controls, but greater for the subgroup of seven male patients as compared with five male controls.

Woods et al. Lousberg et al., and Pain et al used a rebreathing method to assess sensitivity to CO₂. The first study reported that patients with panic disorder were not more sensitive than controls, while the second reported that they were. Pain et al. found no group differences for minute volume, but respiratory frequency increases were greater and tidal volume increases smaller in patients with panic disorder. Gorman et al. obtained results similar to ours for double-breath inhalation of 35% CO₂: patients with panic disorder differed from normal subjects in having more anxiety and higher heart rates before breathing CO₂ but identical rises in anxiety and physiological and biochemical measures.

Although all variables were sensitive to the stressors, the sensitivity of a few may be attributable to factors other than increased emotional activation. Specific physiological reflexes helped determine the response of respiratory variables to CO₂ and of finger pulse amplitude to ice water, and efforts to position the foot properly in ice water probably resulted in body movement in addition to that from pain-induced restlessness. As is usual in studies where multiple psychological and physiological variables are measured, each variable responded to the experimental conditions somewhat differently. Heart rate, impedance trans time, and blood pressure corresponded best to reported anxiety levels, although the exact patterns of correspondence differed. The fact that body movement did not parallel these cardiovascular measures is evidence that they were indexing emotional activation rather than increased physical activity. Our two electrodermal measures, although extremely sensitive to stressors, corresponded poorly to reported anxiety, which suggests they reflect a facet of the emotional reaction to stressors different from what is self-described as anxiety. Unlike in the study of George et al. on effects of lactate and hyperventilation, respiratory sinus arrhythmia increased in normal subjects during stressors. Both CO₂ and hyperventilation increase respiratory tidal volume, complicating the interpretation of respiratory sinus arrhythmia, which reflects a balance between the mechanical effects of greater tidal volume and the presumed vagolytic effects of emotional stress.

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References


