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Autonomic Changes After Treatment of Agoraphobia With Panic Attacks

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Abstract. Twenty-three patients meeting *DSM-III* criteria for agoraphobia with panic attacks and 14 age-, race-, and sex-matched nonanxious controls were tested in the laboratory and on a test walk in a shopping mall. The patients were tested before and after about 15 weeks of treatment with placebo and exposure therapy, imipramine and exposure therapy, or imipramine and initial antiexposure instructions. Controls were tested twice at a similar interval, but without any treatment. On test day 1, patients compared to controls showed higher average heart rate and skin conductance levels and greater numbers of skin conductance fluctuations in the laboratory, and higher heart rates before and during the test walk. Between pretreatment and posttreatment tests, clinical ratings improved and skin conductance levels decreased in all treatment groups. Heart rate levels in the laboratory, on the other hand, decreased in patients on placebo and rose in patients on imipramine. Thus, imipramine compromises the usefulness of heart rate as a measure of emotional arousal. Higher pretreatment heart rates predicted greater clinical improvement.

Key Words. Agoraphobia, panic attacks, heart rate, skin conductance, imipramine.

Agoraphobia with panic attacks is characterized by subjective, behavioral, and somatic symptoms. Since many of the somatic symptoms listed in the *DSM-III* (American Psychiatric Association, 1980) definition of panic-anxiety are signs of autonomic activation or arousal, measures of autonomic activation are likely to be elevated in these patients. Successful treatment would be expected to cause these measures to change in the direction of normality. Furthermore, if the initial values of these measures are related to biological or psychological prognostic factors, they could help to predict treatment outcome (for suggestions as to biological and psychological factors, see Klein, 1981; Margraf et al., 1986).

Here we report the results of psychophysiological testing from 23 agoraphobics with panic attacks who completed at least 8 weeks of a course of treatment with imipramine and/or exposure therapy, out of a group of 37 agoraphobics initially

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recruited and tested. Their results are compared with those from 14 nonanxious, untreated controls who could be tested at intervals similar to those of the agoraphobics, out of an initial group of 19. We measured heart rate and skin conductance levels and reactivity in these agoraphobics and in controls during rest and during the presentation of stimuli with diverse qualities of novelty, startlingness, intensity, and phobicity. Recording was done both in the laboratory and during a behavioral approach test conducted at a local shopping mall. In other articles we have presented in detail pretreatment psychophysiological differences between the initial group of patients and controls (Roth et al., 1986) and clinical effects of treatment in patients who continued into the treatment phase of the study (Telch et al., 1985).

Methods

People suffering from agoraphobia with panic attacks were recruited through advertisements. To participate in the study, subjects had to meet the *DSM-III* definition for agoraphobia with panic attacks. Subjects already in treatment with tricyclic antidepressants or monoamine oxidase inhibitors were excluded. Of the 37 patients originally entering the study, 29 remained for the retesting described below, and the 23 of those with complete physiological test data are the focus of this report. These 23 included only one male, had a mean age of 42 years (range 21-55), and had had agoraphobic fears for a mean of 13.5 years (range 1-34). Two were black.

Controls were also recruited by advertisement. They were selected to match the patients by age, sex, and race, and were paid for their participation. We tried to restrict our control sample to people who were free from psychic complaints, especially ones related to anxiety and phobia. Before testing, subjects were interviewed by a psychiatrist who excluded about a quarter of the applicants for history of anxiety, social phobias, depression, physical symptoms possibly related to anxiety or depression, or signs of anxiety during the interview. An additional subject was rejected because of several high scores on the revised Symptom Checklist-90 (SCL-90) (Derogatis, 1977). Of the 19 controls originally recruited, 14 were successfully retested. These 14 included 2 males and 1 black, and had a mean age of 39 years (range 22-59).

Treatment Design. Patients were matched by scores on the Beck Depression Inventory (BDI) (Beck et al., 1961) and randomly assigned to one of three treatment conditions: imipramine-no exposure; imipramine and intensive therapist-assisted exposure to feared situations; or placebo and therapist-assisted exposure. The imipramine-no exposure group was instructed not to expose themselves unnecessarily to feared situations for the first 8 weeks. After that, they were told to try to enter previously feared situations but were given no therapist assistance. Details of the treatment methods are in Telch et al. (1985). Assessments of clinical change were made at 8 and 26 weeks. Dropouts occurred from all three treatment groups because of adverse reactions to imipramine or to placebo, or to fear of or dissatisfaction with other aspects of the treatment or testing.

Psychological Evaluation. During their pretreatment evaluation, subjects filled out a number of questionnaires including the SCL-90 with a time frame of the past 6 months, the Fear Questionnaire (Marks and Mathews, 1979), the 21-item BDI, and the Zung Self-Rating Depression Scale (Zung, 1965). Patients kept a diary in which they recorded activities and any panic attacks during the study period. The State scale of the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) was given at the time of the laboratory test battery. During the test walk in the shopping center, performance was scored by observers, and subjective anxiety was reported on questionnaires. At 8 and 26 weeks, patients were reevaluated on the test walk and filled out the Fear Questionnaire and the depression questionnaires.

Psychophysiological Testing.

Laboratory battery. Subjects were tested in a battery of four paradigms on 2 separate days. For agoraphobics, day 1 was immediately before treatment and day 2 was after about 4 months of treatment. Controls were retested after a comparable period, but without any intervening treatment. The mean interval between day 1 and day 2 was 15.3 weeks for the patients and 17.9 weeks for the controls.

All subjects were told to discontinue any psychoactive medication 3 days before day 1 of laboratory testing. Only 9 of the 23 were taking such medication daily (6 of those 9 took diazepam, at a mean dose of 14 mg/day). Five of the agoraphobics found total withdrawal from antianxiety agents impossible and had taken anxiolytics within 12 hours of testing. One other had imbibed moderate quantities of alcohol shortly before arriving at the laboratory.

On day 2, the imipramine-no exposure group was taking a mean imipramine dose of 180 mg/day (one subject was averaging < 50 mg/day, while all others were taking ≥ 150 mg/day). The imipramine-exposure group was taking a mean of 200 mg/day (range 150-300 mg/day). The placebo-exposure group was taking capsules equivalent in number to a mean imipramine dose of 165 mg/day (one subject averaged $<$ an equivalent of 50 mg/day, while all the others were taking the equivalent of ≥ 150 mg/day). No subject had imbibed alcohol before testing on day 2, but about five had supplemented their assigned medication with antianxiety agents within 12 hours of testing. These patients were distributed over all three treatment groups.

Testing on the battery took place in a sound-attenuated booth. On day 1, most of the agoraphobics were accompanied to the laboratory by a companion in whose presence they felt reassured and in 8 cases, at the plea of the agoraphobics, their companion was allowed to sit in the booth with them. In these and other cases, agoraphobics often insisted that the door to the booth remain open. On day 2, only two agoraphobics required a companion in the booth. After entering the booth, and before recording began, subjects filled out the State scale of the STAI.

The paradigms were given as follows: (1) *Baseline 1* (5 min). No stimuli were given. Subjects were instructed to sit quietly with their eyes open and to relax. (2) *Habituation* (10 min). This paradigm is a version of the standard orienting response paradigm that has been used in many investigations of psychiatric patients (Öhman, 1981; Bernstein et al., 1982). Nineteen 1-sec tones were given with random interstimulus intervals (ISIs) uniformly distributed over a 24- to 45-sec range. The rise and fall times of the tones were 25 ms. All except tone number 17 were 1000 Hz and 75 dB SPL. Tone 17 was 600 Hz and 70 dB. Subjects were told that they would be hearing tones but that they did not have to do anything. (3) *Intensities* (10 min). This paradigm includes stimuli that have been shown to elicit startle responses (Roth et al., 1984), responses whose biological anlage is distinct from that of orienting responses (Graham, 1979). White noise pips of 50 ms duration with a rise and fall time of 1 ms were given with random ISIs distributed in the range of 12 to 17 sec. The pip intensities were 75, 90, or 105 dB SPL. A total of 37 stimuli was given. The first was 90 dB, and the rest were randomized in 12 groups of 3, each group containing 1 stimulus of each intensity. Subjects were told that they would be hearing noises but that they did not have to do anything. (4) *Baseline 2* (with noise) (5 min). Stimuli were given only during min 3 of the run. The stimuli were 1-sec, 90-dB white noise bursts with 1 ms rise and fall times. A total of 20 were given with a 3-sec ISI from onset to onset of consecutive stimuli. Subjects were told to sit quietly with their eyes closed and to relax. For subjects who had elevated hearing thresholds as determined by audiometry, tone and noise intensities were increased to the degree necessary to make them equivalent to the prescribed SPLs for normal hearing subjects. Methods for recording skin conductance and the electrocardiogram are detailed in Roth et al. (1986).

Ambulatory monitoring. Heart rate was monitored before and during a Behavioral Approach Test (BAT) using a portable microcomputer programmed to store smoothed heart rate averages at 1-min intervals. This device and its use are described in more detail in Taylor et al. (1983). The BAT required the subjects to walk a course consisting of 12 stations through a large shopping mall and to return to the starting point. The stations were shops or other landmarks. A subject who reached all stations would walk a total of 680 m, taking about 10 min.

The computer monitor was attached in the clinic and was worn throughout the BAT. The subjects first sat in a chair in the clinic at least 5 min so that their sitting heart rates could be recorded. Then they were driven to the shopping mall about 10 min away, where they were given a map of the BAT course and oriented to the locations of the stations. At a signal from a timekeeper, they proceeded alone along the course as far as they could go without stopping. At each station reached, they rated their level of anxiety on a 0-10 scale with 0 representing complete calm and 10, extreme anxiety.

Patients performed the BAT with heart rate monitoring before treatment and after 8 weeks of treatment. They repeated it a third time without heart rate monitoring after 26 weeks of treatment. Controls performed the BAT only once and with heart rate monitoring.

Data Analysis.

Laboratory battery. For Baseline 1, the mean skin conductance level (SCL), number of nonspecific fluctuations (NSFs), and mean heart rate level (HRL) were calculated for each of the five 1-min periods. Heart rate variability was calculated for the entire 5-min run. Heart rate variability measures included standard deviations of 10-sec means (bpm) (Heslegrave et al., 1979; Wastell, 1981) and number of reversals calculated on a beat-to-beat basis (Wastell, 1981). More details on these measurements are found in Roth et al. (1986).

For the Habituation and Intensities paradigms, prestimulus SCLs and HRLs and poststimulus evoked skin conductance responses (SCRs) were calculated as explained in Roth et al. (1986). The number of SCRs to habituation was the number of responses before three consecutive failures to respond. Since the stimulus on trial 17 was dishabituating, this measure was only calculated to trial 16.

For Baseline 2, the same measurements were made as for Baseline 1 except for those of heart rate variability, which would be confounded with the effects of the noise.

Ambulatory monitoring. HRLs were calculated for the first 5 min of sitting in the clinic and for as much of the BAT course as the subject completed. Other variables were maximum and minimum HRLs during the BAT; mean, maximum, and minimum anxiety ratings during the BAT; number of stations reached; and mean walking speed.

Clinical variables. Seven psychological variables were selected for statistical purposes as representative of different aspects of the clinical psychological condition of the subject: the Zung Depression Inventory score, the Anxiety score from the SCL-90, the Agoraphobia score from the Fear Questionnaire, frequency of panic attacks/week based on diary information, observed number of stations reached in the shopping center test walk (BAT), and STAI State and Trait scores. Age was added to these seven variables, for a total of eight variables.

Since the Zung score, the Agoraphobia score, and the frequency of panic attacks were available only at 8 and at 26 weeks, a linear interpolation between these time points was made to estimate the values of these variables at day 2.

Statistical Methods. Our analysis had four parts: (1) Because of the large number of potential physiological variables compared to the number of subjects, variables were initially tested for their ability to distinguish patients before treatment from controls. For all variables except for numbers of SCRs, t tests were used. As recommended by Venables and Christie (1980), SCL was transformed before statistical analysis, while HRL was not. Numbers of SCRs were compared by U test. (2) The variables that had distinguished patients and controls were used to examine treatment effects among the three groups of agoraphobics in an analysis of covariance (ANCOVA) with pretreatment (day 1) scores as a covariate. (3) The significance of hypothesized within-group day 2 - day 1 changes in the direction of normalization of patient-control differences were tested with t tests for the selected variables. These tests were made separately for each of the three agoraphobic treatment groups. (4) Product-moment correlations were calculated between clinical and physiological variables at different times.

Results

Pretreatment Differences Between Agoraphobics and Controls. Table 1 summarizes the findings for selected pretreatment psychological variables, and for electrodermal, and heart rate variables. Many variables differed between agoraphobics and controls, the principal exceptions being several SCR and heart rate change variables. For physiological variables the differences were in the direction of higher autonomic activation among the agoraphobics. As we observed before (Roth et al., 1986), there were high positive intercorrelations among HRL variables and among SCL variables. For brevity's sake, the interrelationships of physiological variables are not examined further here.

Treatment and Time Effects. Variables that showed significant agoraphobic-control differences in Table 1 were selected for further testing of differential treatment effects within the agoraphobics. ANCOVAs were performed using day 1 scores as covariates (see Table 2). When the overall F was significant, the adjusted means were compared by t tests in a pairwise manner. HRL variables were markedly affected by treatment, but not in the direction of deactivation. Imipramine raised heart rate equally in the two imipramine treatment groups to levels above those in the placebo group. The effect of treatment on agoraphobia scores barely missed significance ($p < 0.06$).

Figs. 1, 2, and 3 show HRL, SCL, and NSFs from Baseline 1 and Baseline 2 on days 1 and 2. The two imipramine groups are combined. Heart rate levels declined across days in the placebo-exposure group and increased in the imipramine groups. HRL was quite stable within 5-min runs. SCL and NSFs tended to decline during runs and across days, especially in patients. Table 3 addresses the question of whether agoraphobics in the various treatment groups changed significantly in the direction of deactivation on these and other Table 2 variables. The statistics in Table 3 confirm that anxiety and SCL measures moved in the direction of deactivation in all patients, while HRL showed deactivation only in the placebo-exposure group.

Relationships Between Clinical and Physiological Variables. The patterns of these relationships were different for controls and patients. (Note that change scores were calculated as day 2 - day 1.) For *controls,* there were no significant correlations between clinical and physiological variables on day 1. None of the initial levels of the selected physiological variables correlated with change in STAI State score, the only psychological variable taken at two time points in controls. However, the initial STAI State score was correlated negatively with physiological changes between day 1 and day 2 in the HRL variables (e.g., STAI State score vs. change in HRL at Baseline 1 was -0.60, $p < 0.02$, indicating that higher STAI State anxiety was associated with greater HRL decrease between day 1 and day 2.

For *agoraphobics,* the only significant correlations between clinical and physiological variables on day 1 were between Agoraphobia scores and heart rate

Table 1. Means and standard deviations for pretreatment measures

	Controls ($n = 14$)		Agoraphobics ($n = 23$)		
Variable	**Mean**	**SD**	**Mean**	**SD**	***p***
Age	39.5	11.5	41.6	9.87	NS
Agoraphobia	0.82	1.33	34.4	6.18	< 0.001
Zung depression	30.1	8.61	67.2	10.8	< 0.001
PA frequency	0.00	0.00	2.05	1.94	< 0.001
STAIS	30.9	7.72	48.3	8.60	< 0.001
LogSCL-B1	1.32	0.58	1.83	0.58	< 0.05
LogSCL-H	1.06	0.65	1.73	0.53	< 0.01
LogSCL-I	0.99	0.87	1.69	0.51	< 0.01
LogSCL-B2	1.44	0.56	1.78	0.44	< 0.05
Slope LogSCL-B1	-0.12	0.09	-0.03	0.05	< 0.001
Slope LogSCL-H	-0.03	0.02	-0.02	0.02	NS
SCRs to Hab-H	3.64	4.41	5.09	3.96	NS
SCRs-Hi-I	5.71	4.51	7.64	4.04	NS
SCRs-Med-I	3.21	2.49	4.64	3.06	NS
SCRs-Lo-I	1.93	2.13	3.09	2.16	NS
NSFs-B1	9.64	8.34	24.6	21.6	< 0.01
NSFs-B2	6.71	6.33	14.8	10.2	< 0.05
HRL-B1	67.6	6.84	79.8	13.0	< 0.001
HRL-H	66.5	6.78	77.8	12.1	< 0.01
HRL-I	65.3	7.01	78.0	13.0	< 0.01
HRL-B2	64.8	7.81	77.2	12.9	< 0.01
HRVR-B1	18.8	6.02	22.7	6.10	NS
HRV10-B1	1.91	0.65	2.85	1.13	< 0.01
HRL Slope-B1	0.10	0.34	-0.08	0.81	NS
HRL Slope-H	0.03	0.30	-0.05	0.30	NS
BAT stations	12.0	0.00	5.00	3.44	< 0.001
BAT-anxiety	0.01	0.03	5.20	1.93	< 0.001
HRL-A1	79.4	9.48	92.0	14.8	< 0.05
HRL-A2	97.6	13.0	112	13.2	< 0.01
HRL-(A2 − A1)	18.3	10.9	20.7	13.0	NS
Walking speed (m/min)	70.0	8.79	58.0	19.4	NS

Note. Agoraphobia = Agoraphobic scale of the Fear Questionnaire; PA frequency = weekly panic attack frequency; STAIS = State score of the State-Trait Anxiety Inventory. SCL = skin conductance level; NSF = number of nonspecific fluctuations; HRL = heart rate level; HRVR = heart rate variability based on reversals; HRV10 = heart rate variability based on 10-sec epochs; BAT = Behavior Approach Test; B1 = Baseline 1; H = Habituation; I = Intensities; B2 = Baseline 2; A1 = sitting before test; A2 = ambulatory during test. Significance levels for SCRs were determined by *U* test; for other variables, by *t* test (2-tailed).

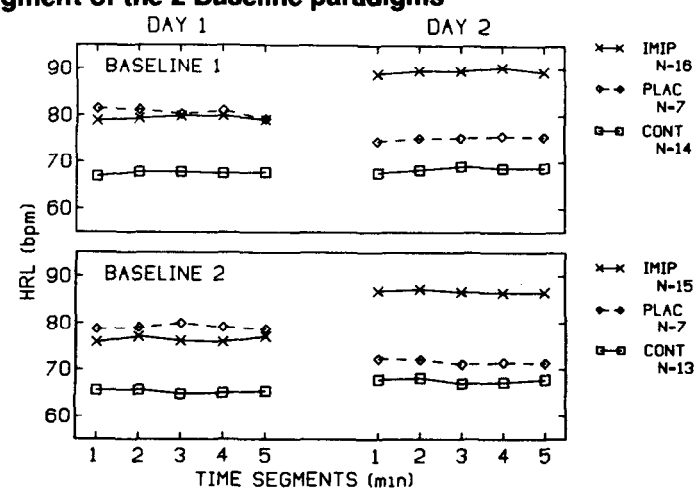
Table 2. Treatment effects for agoraphobics

Variable	Overall treatment effects *F*	Imip vs. Plac-Exp *t*	Imip-Exp vs. Plac-Exp *t*	Imip vs. Imip-Exp *t*
Agoraphobia	3.26			
Zung depression	0.93			
PA frequency	1.26			
STAIS	2.52			
LogSCL-B1	0.41			
LogSCL-H	0.62			
LogSCL-I	1.34			
LogSCL-B2	1.50			
Slope LogSCL-B1	0.27			
NSFs-B1	0.25			
NSFs-B2	2.70			
HRL-B1	6.42[1]	3.21[1]	2.93[1]	0.32
HRL-H	7.63[1]	3.60[1]	3.03[1]	0.61
HRL-I	9.58[1]	4.08[1]	3.22[1]	0.96
HRL-B2	10.13[1]	4.22[1]	3.21[1]	1.25
HRV10-B1	3.11			
BAT stations	2.17			
BAT anxiety	2.15			
HRL-A1	3.30			
HRL-A2	0.28			

Plac-Exp = placebo-exposure; Imip-Exp = imipramine-exposure; Imip = imipramine-no exposure. Other abbreviations for variables as in Table 1.

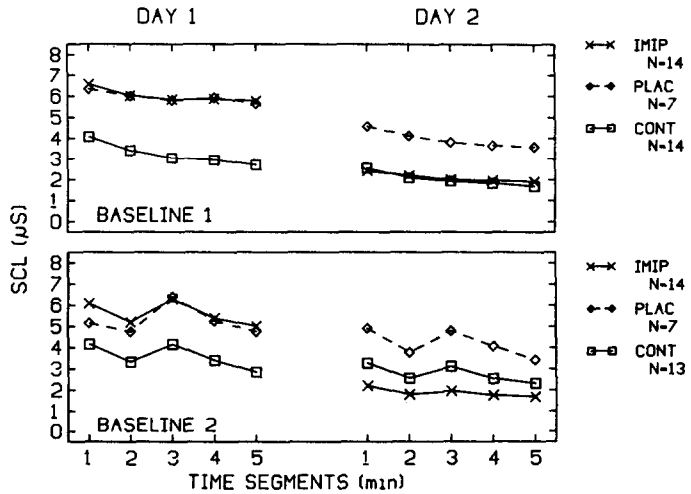
1. $p < 0.01$, 2-tailed.

Fig. 1. Mean heart rate level (HRL) in beats per minute (bpm) for each 1-min time segment of the 2 Baseline paradigms



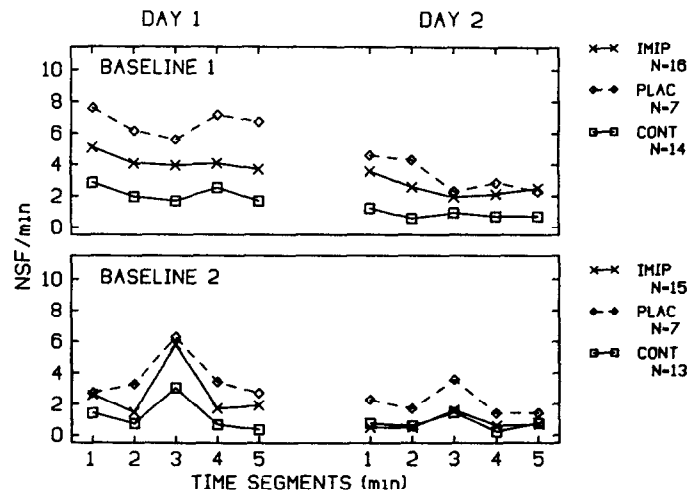
Agoraphobics are divided into those taking imipramine (IMIP) and those taking placebo (PLAC) at day 2. Agoraphobics were not taking medication at day 1, and controls (CONT) did not take medication either day.

Fig. 2. Mean skin conductance level (SCL) in microsiemens (μS) for each 1-min segment of the 2 Baseline paradigms



The groups are explained in the legend for Fig. 1.

Fig. 3. Mean number of nonspecific fluctuations (NSFs) for each 1-min segment of the 2 Baseline paradigms



The groups are explained in the legend for Fig. 1.

variables (e.g., Agoraphobia vs. HRL at Baseline 1, 0.42, $p < 0.03$; vs. ambulatory HRL during the BAT walk, 0.48, $p < 0.02$). Day 1 HRL variables were correlated with changes at 8 weeks in Agoraphobia and with changes at day 2 in STAI State score (e.g., HRL at Baseline 1 vs. change in Agoraphobia, -0.44, $p < 0.02$;

Table 3. Mean within-group changes (day 2 − day 1)

	Groups							
	Control ($n = 14$)		Plac-Exp ($n = 7$)		Imip-Exp ($n = 8$)		Imip ($n = 8$)	
Variable	Mean	p	Mean	p	Mean	p	Mean	p
Agoraphobia			-10.1	< 0.01	-19.4	< 0.01	-6.6	
Zung depression			-9.8		-21.2	< 0.01	-12.6	< 0.01
PA frequency			-0.87	< 0.05	-1.64		-0.31	
STAIS	-1.9		-4.3		-19.4	< 0.01	-8.2	< 0.05
LogSCL-B1	-0.36	< 0.05	-0.47	< 0.05	-0.61	< 0.05	-0.93	< 0.025
LogSCL-H	-0.24		-0.49	< 0.025	-0.72	< 0.01	-0.80	< 0.025
LogSCL-I	-0.23		-0.46	< 0.05	-0.73	< 0.01	-1.10	< 0.01
LogSCL-B2	-0.20		-0.39		-0.83	< 0.01	-0.99	< 0.025
Slope LogSCL-B1	0.055	< 0.025	0.01		0.01		-0.025	
NSFs-B1	-5.5		-16.8	< 0.05	-4.1		-2.1	
NFSs-B2	-2.7		-8.0	< 0.05	-15.5	< 0.01	-2.4	
HRL-B1	0.9		-5.4	< 0.025	6.5		13.6	
HRL-H	1.3		-4.2	< 0.01	8.0		15.2	
HRL-I	1.8		-5.9	< 0.05	5.5		16.2	
HRL-B2	2.2		-7.5	< 0.01	5.6		-17.5	
HRV10-B1	0.25		-0.48		-0.95	< 0.01	1.07	
BAT stations			6.0	< 0.025	5.7	< 0.01	1.6	
BAT anxiety			-2.48	< 0.05	-4.20	< 0.01	-1.39	
HRL-A1			-6.7		-7.0		5.8	
HRL-A2			3.5		5.3		4.0	

Abbreviations for variables as in Tables 1 and 2. The last 4 variables were not measured on day 2 for controls. Significance levels are for changes in the direction of less autonomic arousal as determined by 1-tailed t tests.

ambulatory HRL during walk vs. change in Agoraphobia, -0.56, $p < 0.01$; HRL at Baseline 1 vs. change in STAI State score, -0.39, $p < 0.04$). HRL at Baseline 1 correlated even better with change in Agoraphobia at 26 weeks (-0.64, $p < 0.001$). Thus, higher initial heart rate went along with greater improvement. The correlations between initial Agoraphobia and change in Agoraphobia were smaller: -0.31 at 8 weeks and -0.54 at 26 weeks. Note that all these correlations are for all three treatment groups combined, and hence conceal any treatment-specific effects. Unfortunately, the number of agoraphobics in each treatment groups is so small that no reliable conclusions can be drawn from within-treatment group correlations. It is reassuring that, in some cases at least, these correlations are quite consistent across groups (e.g., for HRL at Baseline 1 vs. change in Agoraphobia at 8 weeks, imipramine-no exposure -0.37; imipramine-exposure, -0.42; and placebo-exposure, -0.49).

With respect to correlations between psychological change scores with physiological change scores, for *controls,* there was a correlation between change in STAI State score and various HRL and skin conductance variables, e.g., with change in HRL during Baseline 1 (0.58, $p < 0.02$), and change in log SCL during Habituation (0.50, $p < 0.04$). For *agoraphobics,* changes in psychological and physiological variables were generally uncorrelated.

Discussion

Before treatment, agoraphobics showed strong evidence of being more activated autonomically than controls, consistent with the pretreatment agoraphobia-control differences reported for the larger samples of which this is a subset (Roth et al., 1986). Tonic measures such as HRL, SCL, and NSF were more sensitive to agoraphobic-control differences than reactivity measures such as number of SCRs or habituation measures such as HRL slope or HRL-(A2-A1). Agoraphobic HRL was higher both inside and outside the laboratory, both before and during exposure to the phobic situation of the mall walk. However, it can also be argued that our tonic measures actually reflected a generalized and perhaps in part anticipatory reactivity: reactivity to a laboratory session that involved phobic elements such as an unfamiliar environment, restraint of movement, and relative isolation from social supports, and reactivity to the disquieting challenge of the mall walk. Another less likely possibility is that the greater activation in agoraphobics was an artifact of their withdrawing from anxiolytic medication. However, fewer than half of the patients were on medication at all, and of the group on anxiolytics, five failed to discontinue their mediction completely before day 1 testing.

Interpretation of changes over time is limited by two factors: (1) We did not have a placebo-no exposure group that could have served as a pure control for time effects unconfounded with treatment effects. (2) Our sample sizes are small. The agoraphobics for whom physiological data were available were divided into three treatment groups, each with fewer than 10 members. If we had had the same sample size as Telch et al. (1985) and our F ratio for Agoraphobia scores had remained the same, our trend toward a differential treatment effect would have reached the 0.05 level as it did in their analysis. Furthermore, our strategy of selecting variables for their ability to distinguish patients and controls still left so many variables that Type I errors may have occurred. We did not try to control this with α level reduction since we were more interested in exploring the properties of different variables than in hypothesis testing.

The one strong treatment effect emerging was a substantial increase in heart rate in groups treated with imipramine, in sharp contrast to clinical and skin conductance variables which tended to normalize in all three treatment groups. The most plausible explanation is that imipramine has a biologial effect on heart rate that operates independently from any effect it has on anxiety. Imipramine is known to have central or peripheral cardiovascular effects that speed the heart (for review, see Goldman et al., 1986). These effects are believed to be related to its anticholinergic properties, which should also influence skin conductance variables. Our data do show a tendency for SCL to decrease more with imipramine than with placebo treatment, but NSFs do not follow this pattern.

The most compelling reason for rejecting psychological explanations for the increased heart rate in the imipramine groups is that such explanations should apply to the placebo-exposure group with the same force. For example, there is no reason to think that anxiety increased between day 1 and day 2 in the imipramine groups but not in the placebo-exposure group. In fact, STAI State scores in all three groups declined—significantly in the imipramine groups. A lack of congruence between

anxiety and HRL changes during initial phases of treatment might be attributed to "desynchrony in measures of fear," which has been reported in several studies (Leitenberg et al., 1971; Hodgson and Rachman, 1974; Mavissakalian and Michelson, 1982; Himadi et al., 1985), but explanations of desynchrony do not fit the imipramine groups better than the placebo-exposure group. For example, desynchrony might be produced if heart rate did not reflect anxiety but instead reflected another psychological variable such as motivation (Fowles, 1982), which was dissociated from anxiety in desynchrony situations. However, any theory that does not accord anxiety a significant influence on heart rate must strain to explain paradigmatic experiments in which heart rate increases in simple phobics as their phobic object is moved nearer to them (Sartory et al., 1977; Nesse et al., 1985).

Perhaps the most interesting correlational finding is that higher pretreatment HRLs predicted more improvement in agoraphobia over time, suggesting that patients whose cardiovascular systems were more emotionally activated improved more. Although correlational results must be regarded as tentative because of their number and the fact that agoraphobics were divided into three treatment groups, this finding was consistent across different HRL measures and generally across treatment groups. A similar finding was reported by Vermilyea et al. (1984): agoraphobics with higher pretreatment HRLs improved more after 12 weeks of cognitive-behavioral treatment without medication than did agoraphobics with lower HRLs. In the same group of subjects, higher pretreatment HRLs also predicted more improvement after 6 months (Craske et al., 1987). One psychological explanation for this relationship is that higher heart rates reflect a stronger evocation of affective memories in provocative situations, which enhances their potential for modification by continued and repeated exposure to these situations (Foa and Kozak, 1986).

In conclusion, nonpsychologically mediated effects of imipramine on heart rate present a serious impediment to assessing emotional arousal by heart rate in imipramine-treated patients. It is conceivable that imipramine's nonpsychological effects could somehow be discounted, allowing the residual emotional heart rate effect to be quantified. At a minimum, this would require individual calibrations in which both drug level and emotional state were varied independently. In the absence of such individual calibrations, attention should be turned to psychophysiological variables other than heart rate. Probably the best candidate among our variables is number of spontaneous skin conductance fluctuations, which can be measured relatively independently from SCL and fluctuation amplitude. In agoraphobics not taking imipramine or other drugs with direct heart rate effects, however, heart rate shows promise as a predictor of therapeutic success.

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