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ORIGINAL PAPER

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Physiological, biochemical and subjective parameters in anxiety patients with panic disorder during stress exposure as compared with healthy controls

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Abstract Physiological (heart rate, blood pressure, electrodermal activity), biochemical (epinephrine, norepinephrine, cortisol) and subjective parameters (self-rating score) of 33 patients with panic disorder (diagnoses according to DSM-III-R) before, during and after stress exposure were compared with those of healthy controls. As stressors a video containing frightening scenes (FS), mental arithmetic (MA), a video documenting a patient suffering from a panic attack (PA) and an improvised speech (IS) were applied. We found significantly higher baseline levels of electrodermal activity (EDA) and norepinephrine (NE) secretion and a subsequent further increase during stress exposure in panic disorder patients as compared with normal controls. The most potent stressors during the trial proved to be mental arithmetics and improvised speech, which was evident in both groups. The situation panic attack video appeared to be a "panic disorder patient-specific" stressor; here we noticed the most pronounced reactions in the patient group. Panic disorder patients had significantly higher self-rating scores of the parameters panicky feelings, anxiety and nervousness at the beginning and throughout the investigation. We conclude that panic disorder patients have a higher degree of activation compared with normal controls, which is evident regarding levels of electrodermal activity and norepinephrine secretion. Furthermore, the panic attack video appears to be a panic disorder patient-specific stressor.

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Introduction

Almost 70 years ago Freud published his classic work on anxiety ("Hemmung, Symptom und Angst", 1926). Ever since, there have been lots of different approaches to this phenomenon. Of particular interest were observations dating back to Aristotle, who correlated subjective anxiety with various physiological parameters (Foster and Humphries 1951). Froberg et al. (1971) postulated the existence of a relationship between physiological reactions of the sympathetic nervous system and the experienced degree of anxiety, whereas the results of other investigators concerning this particular aspect appeared inconclusive (Sarason 1960; Levitt 1967; Pichot 1971; Tyrer and Lader 1976). In a study comparing panic disorder patients and normal controls, Stein and Asmundson (1994) found no differences in their cardiorespiratory or plasma catecholaminergic responses to testing with postural challenge, isometric exercise, cold pressure and Valsalva manoeuver. This contradicted the widespread hypothesis of autonomic dysfunction in panic disorder patients (Bystritsky et al. 1995). Taking the experimental approach one step further, Lacey and Lacey (1958) and Sternbach (1960) began to expose healthy subjects to experimental stressors. This was further facilitated by the introduction of radioenzymatic quantification of epinephrine and norepinephrine in serum and urine (Lake et al. 1976; Weise and Kopin 1976). Raskin (1975) described a slowed response habituation in chronically anxious patients using the skin conductance response, which confirms earlier findings of Lader and Wing (1966). Birket-Smith et al. (1993) also found delayed habituation and high spontaneous skin resistance fluctuations in panic and agoraphobia patients, discriminating them from patients with generalized anxiety disorder. Several publications focused on various physiological and biochemical parameters in anxiety pa-

tients following pharmacological challenge procedures. Gaffney et al. (1988) found no significant changes in cardiovascular parameters pre- and post-sodium lactate infusion comparing panic attack patients and controls. However, emotional complaints within the patient group increased sixfold, indicating that sodium lactate infusion mimicks the physiology of spontaneous panic attacks. Woods et al. (1988) compared panic disorder patients and controls following carbon dioxide exposition. They could demonstrate dose-related increases in anxiety and somatic symptoms in both groups, with significantly higher increases in the patient group. Papp et al. (1993) showed a specific panicogenic effect of carbon dioxide in panic disorder patients (compared with patients with social phobia and normal controls), which was not related to simple breathlessness. Measurements of physiological or biochemical parameters during stress exposure, however, remained scarce (Gasic et al. 1985; Braune et al. 1994).

In our study we looked at differences in reactions between panic disorder patients and control subjects during defined situational arousal and subsequent rest periods. Our aim was to determine if panic disorder patients had different baseline levels of physiological, biochemical or subjective parameters, and if these parameters showed different reactions following stress exposure using a defined situational arousal as compared with healthy controls. Furthermore, we wanted to determine whether certain stressors were specific for patients with panic disorder.

Table 1 Demographic and psychopathological data of patients (n = 33). STAI-X1 anxiety scale (Spielberger 1970); HAMA anxiety scale (Hamilton 1976a); HAMD depression scale (Hamilton 1976b)

Age	38.1 ± 7.1 years	
Gender	14 males, 19 females	
Diagnoses	Panic disorder	14
	Panic disorder with agoraphobia	19
Acute duration of illness	4.2 ± 5.9 years	
Duration of illness	8.1 ± 6.8 years	
Panic attacks per week	2.12 ± 3.04	
Pre-treatment	None	14
	Psychotherapy	5
	Benzodiazepines	10
	β-receptor blocker	6
	Antidepressives	2
	Neuroleptics	1
STAI-X1	52.63 ± 12.14	
HAMA	18.18 ± 4.10	
HAMD	12.94 ± 2.94	

Subjects and methods

Ten healthy subjects (five females and five males) with an average age of 37.1 years (± 8.1 years) on no current medication and without a previous history of any psychiatric disorder participated in the study after giving informed consent. None of those controls consisted of hospital staff nor did any of them have any special knowledge of anxiety disorders or stress testing. Anxiety patients were recruited by means of a newspaper advertisement; there was no payment for this group. All patients were offered treatment independent of their study participation; none of them were on any medication for a minimum of 3 weeks. For further details of the 33 patients including earlier medications see Table 1. The investigation took place in a quiet and comfortable atmosphere. The subjects were seated in an armchair providing easy IV access to a cubital vein (kept open by infusion of normal saline 0.9%), and also to facilitate the completion of the self-rating forms during each rest period. After an initial break of 15 min following IV cannulation, four different stressors were applied, each of them followed by a 3-min recovery phase.The first stressor consisted of a video containing frightening scenes (a tape containing the most dramatic scenes of several movies like "The Shining", "Halloween", "Psycho" and "Rosemary's Baby"), each of them presented with maximum sound volume. During mental arithmetic all subjects had to subtract 7 continuously from 500 until they arrived at the appropriate number as close as possible to zero. The maximum time for this task was 3 min and with every mistake the subjects had to restart at the beginning. This was followed by a second video showing a patient suffering from a panic attack, which lasted approximately 3 min. The last stressor consisted of two parts, first the preparation of and second the delivery of a free speech on one of two topics ("What should be taught during an appropriate sexual education for 12-year-old pupils?" or "What is the influence of contraception on sexual behaviour in adults nowadays?"). In order to increase stress in this situation the subjects had to speak into a microphone and were told that their speech was going to be recorded.

The physiological parameters recorded were heart rate (HR), blood pressure (BP) and electrodermal activity (EDA). The HR and EDA were registered on-line in intervals of 10 s and digitalized using a PCD-2 (Siemens, Erlangen, Germany). Electrodes for HR measurements were placed at the medial part of the right clavicle and the lower left rib cage. The EDA signals were derived from two electrodes placed on the thenar and hypothenar of the

Table 2 Timetable of the investigation. VSS visual self-rating scales; SSR subjective situational ratings; E epinephrine; NE norepinephrine

	Self-rating	Blood samples	Time (min)
Rest period (R 1)	VSS	E, NE, cortisol	15
Video containing frightening scenes (FS)			19
Rest period 2 (R 2)	VSS, SSR	E, NE	22
Mental arithmetics (MA)			26
Rest period 3 (R 3)	VSS, SSR	E, NE	29
Panic attack video (PA)			33
Rest period 4 (R 4)	VSS, SSR	E, NE	36
Improvised speech (IS)		E, NE	39
Rest period 5 (R 5)	VSS, SSR	E, NE, cortisol	46
Rest period 6 (R 6)		E, NE	56
End of investigation	VSS	E, NE, cortisol	61

subjects' left hand. Both tonic and phasic components of the EDA were recorded. Systolic and diastolic blood pressure was measured by the cuff method, and results were recorded once per minute using a polygraphic device.

Biochemical parameters included epinephrine (E), norepinephrine (NE) and cortisol (C); the latter was measured initially, following the improvised speech and during the final rest period; the quantification of cortisol levels was achieved using a radioimmuno assay. Samples for catecholamine measurements were taken initially, following each stressor, and during rest periods 4, 5 and 6 (for details of the timetable see Table 2). All blood samples were immediately put on ice, glutathion (100 µ) added, then centrifuged and stored at –60° C. For quantification a high-pressure liquid chromatography technique with electrochemical detection was used (Ackenheil et al. 1982; Hjemdahl et al. 1979). All subjects were asked to complete a visual self-rating scale (100 mm) initially and during each recovery period comprising the actual degree of panicky feelings, anxiety, nervousness, aggressiveness, muscle tension, exhaustion, perspiration and palpitations. In addition, they were also asked to rate each stressor on a scale containing the following qualities: uncomfortable/comfortable, boring/thrilling, threatening/harmless, strenuous/restful, repulsive/attractive and realistic/artificial.

Patients as well as controls gave their informed consent prior to inclusion in the study. The local ethics committee approved the setup of our investigation, which was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Results

Physiological parameters

Heart rate/blood pressure

Heart rate and blood pressure did not differ significantly between panic disorder patients and controls (see Table 3). During the situations mental arithmetic (MA) and improvised speech (IS) significant increases in heart rate and blood pressure occurred in both groups (HR patients: chi-square 28.23, *dF* 4, $p < 0.0001$; controls: chi-square 20.96, *dF* 4, $p < 0.001$; BP patients: chi-square 36.60, *dF* 4, $p < 0.0001$; controls: chi-square 29.07, *dF* 4, $p < 0.0001$).

Electrodermal activity

Panic disorder patients showed in the beginning, throughout and at the end of the trial higher levels of electrodermal activity as compared with controls (EDA start: *dF* 1,40, $F = 3.46$, $p < 0.05$; EDA end: *dF* 1,40, $F = 4.31$, $p < 0.05$; see Fig. 1; Table 1). MA and IS caused significant increases of EDA in both groups (EDA patients: chi-square 15.35, *dF* 4, $p < 0.01$; controls: chi-square 16.36, *dF* 4, $p < 0.01$). Patients also reacted with an increase in electrodermal activity during the panic attack video, whereas the controls had a decrease in their levels of EDA (*t*-test: $t = 2.20$, *dF* 11.34, $F = 1.75$, $p < 0.05$).

Biochemical parameters

Norepinephrine

Baseline levels of norepinephrine (NE) secretion were significantly higher in panic disorder patients as compared with the control group (patients: x = 318.31, SD = 89.82; controls: x = 235.70, SD = 53.04; *dF* 1,40; $F = 7.04$; $p < 0.01$; see Fig. 2; Table 3). At the end of the trial we could no longer demonstrate any significant difference between the two groups. This was the result of a continuous increase of NE secretion, measured during each of the recovery phases in the control group (chi-square 10.44, *dF* 3, $p < 0.01$), whereas the patients maintained their higher level throughout the duration of the investigation.

Epinephrine

No significant difference between panic disorder patients and controls could be shown comparing the initial level of epinephrine (E) to the level at the very end (Table 3). In terms of this parameter mental arithmetics appeared to be an exclusive stressor for the patients, whereas the improvised speech caused a significant increase in epinephrine secretion only in the controls.

Cortisol

Values of cortisol secretion (Table 3) did not differ significantly between panic disorder patients and controls in the beginning (R 1 = pre-stress exposition) and in the end (R 6). A significant reduction in cortisol levels was present in both groups over the duration of the trial (patients: chi-square 18.73, *dF* 1, $p < 0.01$; controls: chi-square 6.4, *dF* 1, $p < 0.01$).

Subjective ratings

Visual self-rating scales (VSS)

Patients had significantly higher levels of panicky feelings according to the self-rating scale at the beginning of the test (ANOVA: *dF* 1,38; $F = 3.81$; $p < 0.05$; see Fig. 3). This difference was no longer present at the very end. Comparing the initial and final values of panicky feelings a significant reduction could be demonstrated over the trial, which was due to a lower degree of panic in the panic disorder group after the improvised speech (MANOVA: *dF* 4,140, $F = 2{,}61$, $p < 0.05$).

For details of all subjective parameters see Table 3.

Regarding the quantity of anxiety feelings, using ANOVA, patients had higher levels at the beginning and at the end as compared with controls (beginning: *dF* 1,38, $F = 8.04$, $p < 0.01$; end: *dF* 1,38, $F = 4.01$, $p < 0.05$; see Fig. 4).

A similar situation was encountered for the subjective rating of nervousness: at the initial and at the final rest pe-

Table 3 Physiological, biochemical and subjective variable [mean (m) and standard deviation (SD)] during all rest periods and stressor situations for anxiety patients and controls

			R1	FS	R2	MA	R3	PA	R4	IS	R5	R6
HR	Patients	m	79.88	86.43	80.57	92.74	79.18	82.05	78.53	92.52	79.98	76.86
		SD	12.03	14.35	10.72	13.32	10.65	12.91	10.85	15.97	9.71	9.01
	Control	m	75.65	79.95	77.44	90.92	76.38	85.25	76.78	96.59	77.97	77.53
		SD	8.49	8.95	7.00	11.90	6.99	16.57	7.37	16.21	7.37	7.24
EDA tonic	Patients	m	14970.69	17052.087	16613.032	18170.84	17955.32	18772.16	18560.50	20832.37	20617.09	20725.088
		SD	9153.97	9141.20	9485.05	9524.14	10484.77	10796.16	11128.77	12193.68	12262.03	12399.085
	Controls	m	9572.65	11298.022	10956.085	13659.15	11593.91	10725.48	11249.35	14092.16	11936.15	12001
		SD	5793.43	6760.69	5545.53	6801.98	5685.20	5940.37	6518.99	6870.06	5702.57	6165.40
EDA phasic	Patients	m	322.56	723.44	266.41	650.59	358.86	447.17	293.12	532.58	494.62	399.56
		SD	276.86	531.94	187.13	412.06	287.20	326.59	190.81	503.63	337.46	246.23
	Controls	m	131.39	696.32	122.01	1028.42	176.55	130.02	219.60	686.85	390.46	365.29
		SD	168.44	450.08	95.41	717.08	169.48	126.96	234.38	465.85	221.06	428.58
BP systolic	Patients	m	116.66	124.43	118.75	140.54	121.61	123.34	115.09	134.88	116.85	115.58
		SD	11.93	10.96	12.02	16.72	15.63	13.15	10.73	12.68	11.76	10.42
	Controls	m	112.50	118.89	110.00	130.83	113.61	116.94	112.78	142.22	113.33	113.89
		SD	13.17	16.72	10.89	20.31	11.66	14.61	9.79	17.65	12.11	12.56
BP diastolic	Patients	m	80.45	83.10	80.29	85.88	82.14	82.32	80.98	86.42	82.13	81.73
		SD	12.00	8.60	9.20	11.70	8.97	8.94	9.34	11.68	8.76	8.59
	Controls	m	74.50	77.78	77.78	83.33	77.22	78.06	77.50	88.89	76.11	77.50
		SD	11.16	10.85	10.18	17.41	10.11	11.02	8.19	12.69	8.57	8.00
Norepinephrine	Patients	m	318.31	333.02	–	332.42	–	331.34	322.03	345.59	343.84	333.34
		SD	89.82	105.94	–	198.23	–	89.64	87.50	89.13	123.55	99.79
	Controls	m	235.70	234.60	–	256.70	–	256.50	272.50	323.50	288.10	274.60
		SD	53.04	60.19	–	62.46	–	75.80	76.26	108.43	103.86	57.05
Epinephrine	Patients	m	56.63	63.15	–	75.05	–	56.84	61.00	61.89	54.31	50.94
		SD	24.87	41.41	–	29.24	–	28.25	41.67	23.95	22.33	20.43
	Controls	m	59.70	53.10	–	68.70	–	52.50	57.00	72.40	64.30	61.50
		SD	28.87	22.12	–	23.79	–	27.17	42.52	48.54	52.84	35.99
Cortisol	Patients	m	18.73	–	–	–	–	–	–	15.94	–	14.83
		SD	6.75	–	–	–	–	–	–	6.52	–	5.40
	Controls	m	16.59	–	–	–	–	–	–	13.61	–	13.05
		SD	6.00	–	–	–	–	–	–	5.14	–	5.52
VSS panicky feelings	Patients	m	26.96	27.25	–	34.18	–	30.84	–	25.62	–	13.30
		SD	25.28	25.62	–	29.33	–	26.95	–	22.41	–	18.78
	Controls	m	9.30	6.60	–	14.20	–	5.30	–	7.20	–	5.22
		SD	11.30	4.55	–	18.77	–	5.22	–	10.00	–	5.44
VSS anxiety	Patients	m	34.97	39.25	–	35.24	–	38.87	–	29.94	–	18.13
		SD	24.78	30.92	–	28.50	–	29.40	–	25.93	–	19.95
	Controls	m	10.67	7.30	–	12.00	–	4.90	–	7.90	–	4.78
		SD	11.30	7.05	–	14.58	–	3.21	–	10.50	–	4.35
VSS nervousness	Patients	m	44.82	47.38	–	53.64	–	45.09	–	46.42	–	32.50
		SD	22.27	19.19	–	28.35	–	29.67	–	29.20	–	24.77

Table 3 (continued)

			R1	FS	R2	MA	R3	PA	R4	IS	R5	R6
	Controls	m	24.11	12.50	–	25.10	–	15.10	–	17.24	–	8.00
		SD	20.69	14.14	–	20.42	–	14.27	–	13.99	–	7.95
VSS aggressiveness	Patients	m	13.09	21.31	–	19.76	–	12.15	–	14.27	–	11.17
		SD	18.20	23.55	–	23.80	–	14.19	–	17.06	–	18.62
	Controls	m	6.78	9.10	–	9.40	–	5.40	–	5.80	–	4.33
		SD	6.47	9.79	–	10.13	–	4.92	–	5.65	–	5.00
VSS muscle tension	Patients	m	27.24	32.25	–	33.36	–	32.91	–	30.97	–	25.80
		SD	22.66	27.61	–	26.25	–	26.51	–	25.55	–	25.11
	Controls	m	11.22	13.80	–	20.00	–	13.80	–	14.10	–	9.11
		SD	10.38	14.52	–	18.53	–	13.55	–	14.46	–	8.69
VSS exhaustion	Patients	m	23.21	23.56	–	37.60	–	28.58	–	35.46	–	33.83
		SD	21.60	18.22	–	27.12	–	24.16	–	27.30	–	25.04
	Controls	m	5.56	6.30	–	10.90	–	4.60	–	7.00	–	4.44
		SD	4.49	3.62	–	10.51	–	3.92	–	6.60	–	3.39
VSS sweating	Patients	m	25.69	26.19	–	29.58	–	28.85	–	31.40	–	20.77
		SD	23.53	19.61	–	25.43	–	25.00	–	25.97	–	21.62
	Controls	m	29.11	19.40	–	21.00	–	15.00	–	17.50	–	15.89
		SD	25.93	15.16	–	16.20	–	13.47	–	12.53	–	13.68
VSS palpitations	Patients	m	25.52	34.81	–	31.15	–	32.67	–	28.30	–	19.60
		SD	20.51	25.95	–	24.16	–	24.42	–	24.56	–	19.53
	Controls	m	16.11	21.30	–	21.00	–	17.90	–	15.90	–	9.67
		SD	15.65	15.60	–	17.04	–	14.01	–	13.65	–	10.78
SSR uncomfortable/ comfortable	Patients	m	–	23.13	–	29.88	–	25.64	–	27.39	–	–
		SD	–	21.16	–	21.82	–	17.67	–	20.84	–	–
	Controls	m	–	25.30	–	36.25	–	39.50	–	48.20	–	–
		SD	–	18.00	–	22.75	–	22.69	–	29.45	–	–
SSR threatening/ harmless	Patients	m	–	35.22	–	63.70	–	40.82	–	53.67	–	–
		SD	–	26.05	–	30.87	–	25.93	–	30.10	–	–
	Controls	m	–	54.90	–	85.13	–	70.20	–	68.00	–	–
		SD	–	33.95	–	10.49	–	24.46	–	23.17	–	–
SSR strenous/ restful	Patients	m	–	30.59	–	30.00	–	37.02	–	25.12	–	–
		SD	–	18.12	–	20.21	–	21.19	–	17.31	–	–
	Controls	m	–	32.70	–	26.50	–	42.10	–	35.60	–	–
		SD	–	14.46	–	23.06	–	19.77	–	21.72	–	–
SSR boring/ thrilling	Patients	m	–	48.44	–	57.33	–	47.67	–	53.36	–	–
		SD	–	27.64	–	24.87	–	21.31	–	23.01	–	–
	Controls	m	–	42.70	–	59.38	–	44.60	–	67.40	–	–
		SD	–	28.25	–	21.22	–	22.98	–	12.97	–	–
SSR repulsive/ attractive	Patients	m	–	16.22	–	45.45	–	37.18	–	52.67	–	–
		SD	–	19.43	–	20.67	–	15.53	–	15.40	–	–
	Controls	m	–	23.00	–	52.75	–	41.00	–	56.30	–	–
		SD	–	21.56	–	19.59	–	12.06	–	19.14	–	–
SSR realistic/ artifical	Patients	m	–	76.81	–	38.06	–	25.15	–	29.42	–	–
		SD	–	26.99	–	25.45	–	22.81	–	21.73	–	–
	Controls	m	–	82.10	–	40.63	–	30.00	–	41.20	–	–
		SD	–	18.66	–	24.33	–	31.53	–	26.41	–	–

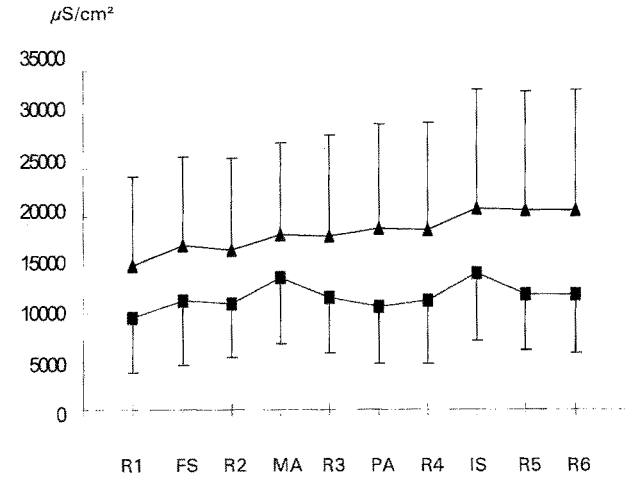

Fig. 1 Electrodermal activity (in µS/cm2) in 32 patients with panic disorder (*triangles*) and 9 controls (*squares*) during rest and defined stress exposure. *R* rest; *FS* frightening scenes; *MA* mental arithmetic; *PA* panic attack video; *IS* improvised speech. (For details see text)

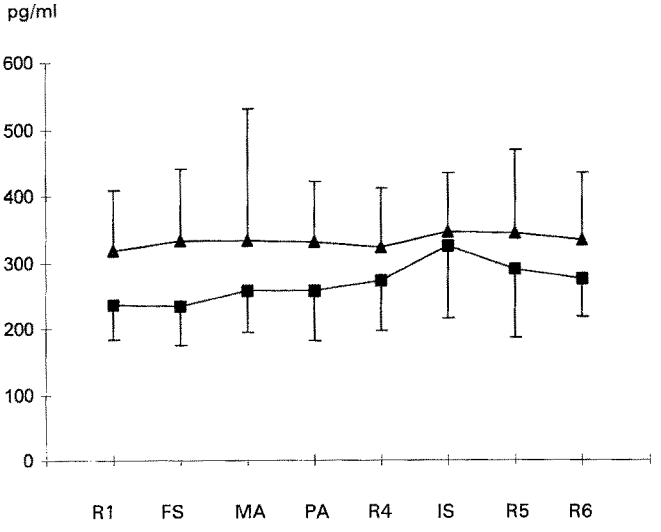

Fig. 2 Norepinephrine levels (in pg/ml) in 32 patients with panic disorder (*triangles*) and 10 controls (*squares*) during rest and defined stress exposure. (For details see text)

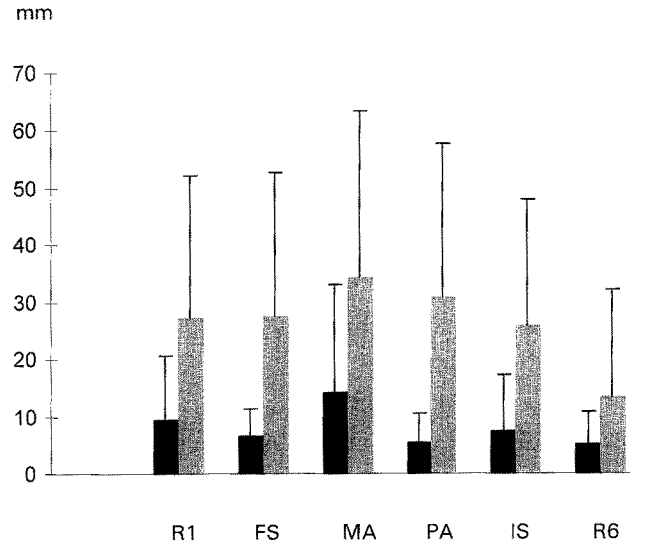

Fig. 3 Self-rated panicky feelings in 30 patients with panic disorders (*grey*) and 10 controls (*black*) during rest and defined stress exposure. (For details see text)

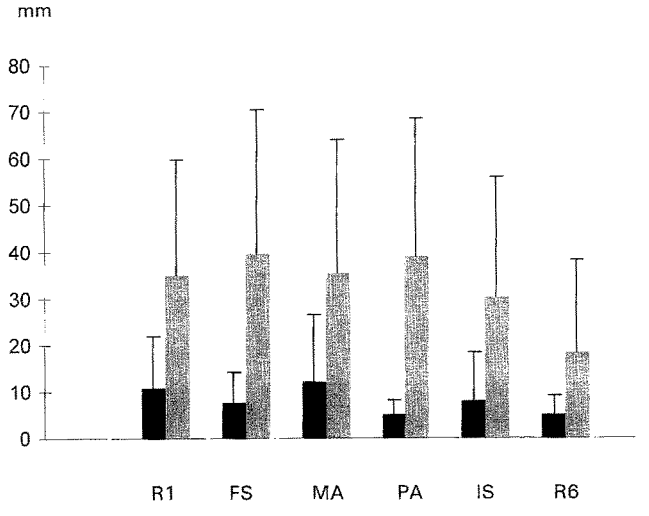

Fig. 4 Self-rated anxiety feelings in 30 patients with panic disorders (*grey*) and 10 controls (*black*) during rest and defined stress exposure. (For details see text)

riod levels were significantly higher in panic disorder patients than in controls (R 1: dF 1,38, $F = 5.32$, $p < 0.05$; R 6: dF 1,38, $F = 8.88$, $p < 0.01$; see Fig. 5).

The degree of muscle tension as well as that of exhaustion was higher in the patient group according to their self-rating scores (muscle tension, R 1: dF 1,38, $F = 4.36$, $p < 0.05$; R 6: dF 1,38, $F = 3.96$, $p < 0.05$; exhaustion, R 1: dF 1,38, $F = 6.03$, $p < 0.05$; R 6: dF 1,38, $F = 11.66$, $p < 0.01$).

Subjective situational ratings (SSR)

The video containing frightening scenes was rated as the most uncomfortable, threatening and repulsive situation by patients and controls. The most strenuous situation for controls was mental arithmetic, and for patients, improvised speech. Using ANOVA, panic disorder patients rated the panic attack video and the improvised speech as significantly more uncomfortable as compared with controls (PA: dF 1,39, $F = 4.68$, $p < 0.05$; IS: dF 1,39, $F = 7.55$, $p < 0.01$). Patients perceived the panic attack video and mental arithmetic as significantly more threatening (PA: dF 1,39, $F = 8.22$, $p < 0.01$; MA: dF 1,39, $F = 4.02$, $p < 0.05$). The improvised speech was rated as significantly more strenuous by the patients (IS: dF 1,39, $F = 4.05$, $p < 0.05$).

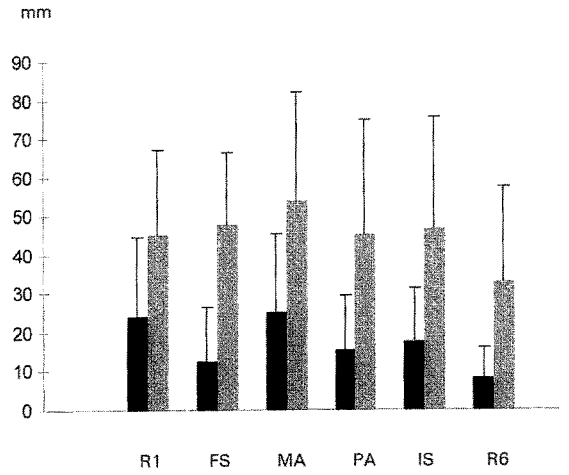

Fig. 5 Self-rated nervousness in 32 patients with panic disorders (*grey*) and 10 controls (*black*) during rest and defined stress exposure. (For details see text)

Discussion

Initial values

Heart rate did not reveal a significant difference between panic disorder patients and controls, which corresponds to the results of most authors (Braune et al. 1994; Charney et al. 1984; Cowley et al. 1987; Freedman et al. 1985; Gasic et al. 1985; Gaffney et al. 1988; Mathews et al. 1982; Villacres et al. 1987; Yeragani et al. 1987; Woods et al. 1987; Stein et al. 1992; Stein and Asmundson 1994; Bystritsky et al. 1995). Perception of heart rate appears to be different as Ehlers et al. (1992) reported in their findings, i.e. panic disorder patients showed an increased awareness of their heart beats compared with other anxiety patients. Recently, an altered heart rate variability in panic disorder patients was described (Rechlin et al. 1994; Klein et al. 1995; Middleton and Ashby 1995). Other investigators found a higher heart rate in those patients (Altschule 1953; Bond et al. 1974; Wing 1964; Hart 1974). The main reason for this discrepancy is supposed to be a difference in study design and in the duration of the drug-free interval. In our study we accomplished a 3-week interval without medication, Fagerström (1985) used a wash-out period of 1 week, and King et al. (1987) permitted self-medication using benzodiazepines during an otherwise drug-free period of 3 weeks.

Values for systolic and diastolic blood pressures did not differ in the two groups, which demonstrates that there is no baseline activation of the cardiovascular system in panic disorder patients. In contrast to these findings, diastolic blood pressure has been suggested to be a discriminatory factor between panic patients and controls (Bystritsky et al. 1995).

The baseline levels of the electrodermal activity were significantly higher in the patient group, which is compatible with the findings of other investigators (Albus et al. 1987; Bond et al. 1984; Cowley et al. 1987; Freedman and Glass 1984; Lader and Wing 1966; Roth et al. 1986; Roth et al. 1990; Birket-Smith et al. 1993; Braune et al. 1994). No such differences could be confirmed according to several other publications (Freedman et al. 1984; Gasic et al. 1985; Mathew et al. 1982; Villacres et al. 1987; Woods et al. 1987; Yeragani et al. 1987). It has to be considered that in most studies (Lader and Wing 1966; Bond et al. 1974; Roth et al. 1986) measurements were taken in a single session. If one accepts the electrodermal activity as an indicator of reactions of orientation (Fahrenberg 1979), one would have to expect that the unfamiliarity of the experimental design leads to an increase in the electrodermal activity system.

In line with previous stress exposure studies (Albus et al. 1987), the panic disorder patients showed significantly higher resting levels of norepinephrine. This confirms the findings of several other studies (Ballenger et al. 1984; Mathew et al. 1981; Nesse et al. 1984; Braune et al. 1994). In contrast, Gasic et al. (1985), Kralik et al. (1982), Villacres et al. (1987) and Stein et al. (1992) did not find significant differences comparing the NE secretion of anxiety patients and normal controls. Although the abovementioned studies are comparable concerning the timing of blood sampling and laboratory tests, important differences exist in terms of the composition of the patient groups according to the diagnosis and the modalities of blood specimen sampling (arterial vs venous sampling), which might well explain different results. The latter item was dealt with in an investigation by Hjemdahl et al. (1984) who found significant differences between arterial and venous blood sampling in the forearm, where approximately 45% of the venous norepinephrine derived from the forearm tissue. Looking at those results modifications of the experimental design can influence the outcome; on the other hand, the question arises as to whether the "peripheral" parameter norepinephrine has any diagnostic value quantifying central, psychic phenomena in panic disorder patients.

The baseline levels of epinephrine secretion did not show significant differences between panic disorder patients and controls. Similar results were published by Gasic et al. (1985), Kralik et al. (1982), Mathew et al. (1982) and Braune et al. (1994). Also Cameron et al. (1987) found no increases in serum epinephrine levels in panic disorder patients monitored over a duration of 24 h. This seems to confirm that there is no disturbance of the medullary component of the adrenergic system in panic disorder patients.

Also for the secretion of cortisol no significant differences between patients and controls were found. This is in accordance with the findings of Charney and Heninger (1985) and Woods et al. (1987, 1988). There seems to be no alteration of function regarding the axis hypothalamus–hypophysis–adrenal marrow in panic disorder patients.

In terms of the visual self-rating scales (VSS) of panicky feelings, anxiety, nervousness, muscle tension and exhaustion we could demonstrate significantly higher levels in panic disorder patients as compared with controls.

This is primarily due to an increased anticipatory anxiety, which by itself can be an important contributory factor in panic provocation (Roth et al. 1992). Furthermore, most of the above-mentioned criteria belong to the diagnostic criteria of anxiety disorders and would therefore be expected to be higher anyway when compared with healthy controls. A variety of other investigators have published similar findings (Braune et al. 1994; Charney and Heninger 1985; Charney et al. 1984, 1987; Ehlers et al. 1986; Freedman et al. 1984; Griez et al. 1987; Gorman et al. 1988; Nesse et al. 1984; Rainey et al. 1984; Woods et al. 1988). Since this difference is present already prior to the stress exposure, panic disorder patients appear to have a higher degree of anticipatory anxiety as compared with normal controls.

Situational effects

During the video containing frightening scenes, where a passive tolerance of auditive as well as visual stressors is required, no significant differences in terms of the physiological and biochemical parameters comparing the two groups could be found. The statistically nonsignificant increase in heart rate, blood pressure and electrodermal activity was in line with the finding of Spinks and Siddle (1985), Lawler (1980) and Erdmann et al. (1984).

The two stressors mental arithmetic and improvised speech led to pronounced reactions regarding most parameters in both groups, with the most striking increases taking place during the improvised speech. During the latter situation we found the peak values of heart rate, blood pressure and electrodermal activity in the panic disorder patients as well as in the controls. In addition, the most pronounced increases in epinephrine and norepinephrine secretion were shown for the control group during IS. These results are in line with the findings of other investigators (Erdmann et al. 1984; Schmidt et al. 1994; Baltissen and Boucsein 1987; Houtman and Bakker 1987). Whereas Taggart et al. (1973) found isolated and significant increases in norepinephrine secretion in healthy controls during an improvised speech, Dimsdale and Moss (1980) report during the same set-up an isolated increase in epinephrine secretion at the beginning of the speech, which was no longer present at the very end of it. Referring to those results the timing of catecholamine sampling during the course of any stressor seems important in relation to the resulting value. According to those findings epinephrine appears to be the quicker and more sensitive parameter regarding stress exposition. Marked increases in epinephrine secretion for both groups were documented during mental arithmetic, which corresponds to the findings of Bonelli et al. (1979), Forsman and Lindblad (1983), Albus (1984) and Albus et al. (1982, 1986). In our study norepinephrine increased only nonsignificantly in the control group, and no changes were seen in the patient group (see Fig. 2).

It is interesting to note that the increase in electrodermal activity during the improvised speech took place during the preparation period, whereas the increase in the cardiovascular parameters followed during the speech itself. This sequence of events was observed for patients as well as for controls. A possible explanation would be the theory that the anticipation of a potential stressor leads exclusively to an increase in electrodermal activity, whereas the actual confrontation with a stressor provokes an activation of the cardiovascular system. This is in line with the theories of Lacey (1967), who postulates a nonspecific activation during situations of anticipation and a specific cardiovascular activation just prior to the actual reaction itself.

During the previously described situations the parameters of patients and controls did both change accordingly, i.e. either increased or decreased. During the panic attack video no significant changes could be demonstrated for either cardiovascular or biochemical parameters. The control group did show lower levels of electrodermal activity, whereas patients had a significant increase in that parameter as compared with the previous rest period. The panic attack video appears to be an "anxiety-specific" stressor; certainly, the knowledge of self-experienced and potentially future panic attacks led to a more potent stressor effect in panic disorder patients. The latter group, especially after having experienced panic attacks themselves, did show a significant increase in epinephrine secretion, EDA and subjective parameters, particularly in situations which cause associations with panic attacks (Markgraf et al. 1986).

Regarding the parameters heart rate and blood pressure during the final rest period (R 6) no significant differences could be found comparing patients and controls, but the former had significantly higher levels of electrodermal activity at the very end of the trial. During the course of our experiment both groups showed continuously increasing values of EDA, more so in the patient group. Apparently, rest periods of 4-min duration, which proved sufficiently long in similar stress investigations in healthy controls (Fahrenberg et al. 1979), were too short for the group of panic disorder patients to return to their baseline levels of electrodermal activity. We therefore have to assume that panic disorder patients not only have higher levels of EDA, but also a delayed habituation following stimulation, which leads to a postponed return to baseline levels after stress exposure. This is in line with the findings of Raskin et al. (1975) and Horvath and Meares (1979) who confirmed a delayed return to normal levels following stress exposure in anxiety patients.

The norepinephrine secretion of the controls did continuously increase over the duration of the trial. During the final rest period no significant difference between the two groups could be shown any longer. The reason for this can be seen in high initial levels of secretion in the patient group. Apparently, a "ceiling effect" is reached in the patient group, which renders a further activation of the noradrenergic system impossible (Wilder 1931).

In both groups decreasing levels of cortisol secretion were noticed during the course of the entire experiment, which confirms the findings of Herbert and Watts (1986).

They found peak levels of cortisol secretion just prior to the start of mental stressors, and thereafter, declining values. It has to be kept in mind that our investigation took place during the late morning, when cortisol secretion is decreasing anyway due to the circadian rhythm. In order to comment on the effect of specific stressors upon the level of cortisol secretion, a modified experimental design relating to the number of measurements and their timing would be required.

Subjective ratings

Panicky feelings were significantly higher in the patient group at the beginning and during the course of the investigation. Only at the very end, following the improvised speech, did they approach the level of the control group, no longer showing any significant difference. A similar picture was recorded for the subjective anxiety feelings. Significantly higher levels in the patient group were documented until the final rest period. Patients also had persistently higher ratings for the parameter nervousness. Both groups became gradually less nervous during the course of the investigation. Higher ratings in the anxiety patient group for the above criteria were also found by Woods et al. (1988) who compared patients with panic attacks to healthy controls.

Comparing the different stressors the video containing frightening scenes proved to be the most uncomfortable, threatening and repulsive situation for panic disorder patients and controls. According to the hypothesis of Lader (1982) this is to be expected. This author postulated a strong anxiogenic potency in situations where probands have to passively tolerate aversive, external stimuli.

Despite the fact that the improvised speech was the most strenuous situation for the patient group, the level of norepinephrine secretion increased during the latter only minimally, whereas that of epinephrine decreased. Initially high values of catecholamine secretion due to a high level of anticipatory anxiety seemed to make a further activation of the adrenergic and noradrenergic system impossible, which again is described as a kind of "ceiling effect" (Wilder 1931; Fahrenberg 1979). In contrast, Ward et al. (1983) and Dimsdale and Moss (1980) found increases in epinephrine secretion during the application of mental stressors in healthy controls, whereas physical exercise induced mainly increased levels of norepinephrine secretion. This is confirmed by the hypothesis of Frankenhaeuser (1975), according to which situations of novelty, anticipation and unforeseenness cause increases in epinephrine secretion, whereas physical exercise leads predominantly to higher levels of norepinephrine.

The panic attack video was rated to be fairly thrilling by the controls, panic disorder patients perceiving this situation as much more threatening and strenuous. The reason for this seems to be previous experience of panic attacks. This very situation appears to be a "panic disorder patient-specific stressor".

Conclusion

Panic disorder patients had higher levels of electrodermal activity and of norepinephrine secretion at the beginning, during exposure to various different stressors and at the end of our stress experiments when compared with healthy controls. The other physiological and biochemical parameters were not statistically different between the two groups. The most efficient stressors during the trial proved to be mental arithmetic and improvised speech, which produced similar reactions in both groups. This was quite different from the effects of showing the panic attack video, where we noticed most pronounced reactions in the panic disorder patient group (EDA, subjective ratings). This stress exposure design was shown to provoke reactions specifically in panic disorder patients.

Subjective–verbal parameters were quite markedly increased in panic disorder patients, most strikingly so with regard to anxiety, panicky feelings and nervousness. During exposure to stress the kind of stressor applied had apparently only a minor effect upon the subjective ratings.

Panic disorder patients were shown to have higher levels of norepinephrine, electrodermal activity and subjective ratings already prior exposure to stress. We conclude that this represents the somatic correlate of an increased anticipatory anxiety in panic disorder patients.

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