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Psychophysiological Reactivity under Mental Stress in Atopic Dermatitis

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Key Words
Atopic dermatitis · Parasympathetic activity · Psychophysiology · Stress · Sympathetic activity

Abstract
Background: An association of mental stress with atopic dermatitis is widely accepted. However, no long-term evaluation of psychophysiological reactivity over the course of disease has yet been performed. ***Objective:*** We examined whether atopic dermatitis patients have an increased psychophysiological reactivity compared to healthy controls and in between acute and disease-free phases, and whether they differ in psychological state and trait variables. ***Methods:*** Fifteen patients with atopic dermatitis underwent a stress test during acute exacerbation and after symptom improvement and were compared to matched controls. ***Results:*** Psychophysiological responses to stress were not stronger in the patient group than in the controls. Nevertheless, the patients had a higher heart rate and lower vagal activity throughout the resting and stress phases at both examination times. The patients showed significantly higher anxiety, depression and emotional excitability, and self-ratings of inactivity clearly distinguished acute phases from remission. ***Conclusion:*** There is an increased vegetative excitability level in patients with atopic dermatitis, which cannot be attributed solely to increased disease activity.

Introduction

Atopic dermatitis (AD) is a chronic or relapsing skin disease, characterized by pruritus, the typical morphology and distribution of disseminated erythematous papules and pustules in the acute eczematous phase and of dry or lichenified patches of skin in the chronic phase, and other atopic manifestations (such as asthma or seasonal allergies) in the personal or family history [1]. The pathogenesis of AD has not been fully elucidated to date. Among the pathogenic concepts are genetic influences, structural anomalies (dry skin), abnormalities in cellular immunity and increased IgE production. A dysregulation of the autonomic nervous system as well as psychosomatic influences are prominent features as well [2, 3]. A growing number of reports support the role of psychological stress in AD [4]. The majority of AD patients report a direct association between onset/flare of their lesions and stressful life events. Case studies have reported stress, tension, exhaustion of coping mechanisms, mention of emotionally charged topics and object loss as possible triggers [5]. Psychodiagnostic tests reveal increased levels of anxiety and depression in AD patients [5, 6]. Also, conditions that manifest with irritability, anger and depression, such as the premenstrual syndrome in female patients, have been related to skin deterioration in AD [7]. It remains unclear, though, whether an internal conflict predates an exacerbation or whether the disease itself leads to an increased psychological pressure.

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The apparent close relationship between psychological stress and cutaneous inflammation in AD has led to the speculation that the sympathetic nervous system is linked to the manifestation of AD. One of the body's reactions to stressful stimuli is an activation of the sympathetic nervous system and release of catecholamines. Indeed, there is increasing evidence that the sympathetic nervous system plays a role in the modulation of general and cutaneous immune responses [8–11]. The postulated autonomic dysregulation and the immunological abnormalities in AD may be linked in several ways. Usually, catecholamines increase cAMP levels after binding to their receptors on immune cells, but in AD patients, leukocytes display an increased phosphodiesterase activity, leading to low levels of cAMP [12, 13] and the release of mediators such as histamine, prostaglandin and leukotrienes [14]. These mediators trigger itch and inflammation in atopic individuals. Furthermore, catecholamines can skew the immune response towards the Th2 phenotype [15], and the initiation of AD appears to be driven by an allergen-induced activation of Th2 cells [16]. The finding that CD8+ T lymphocytes counts are increased for 1 h after mental stress in patients with AD compared to healthy controls due to elevated norepinephrine plasma levels further supports the notion of neuroimmunological mechanisms in AD [17]. Finally, neurotransmitters, such as substance P, calcitonin gene-related peptide, somatostatin and others, have been linked to pruritus and neurogenic inflammation in skin diseases [18], particularly AD [19, 20].

These observations have led investigators to examine whether AD patients have a greater autonomic arousal during stressful situations [21–23]. While two earlier studies suggested a psychophysiological component in AD, the latter did not support this assumption, possibly because the investigators used different experimental settings and did not distinguish phases of activity and inactivity of AD. Thus, in the present study, we re-examined the postulated increases in stress reactivity in AD patients versus control subjects and, in addition, compared psychoreactivity in acute episodes versus disease-free phases. Measures of psychophysiological activity were cardiac sympathetic activity (heart rate), cardiac parasympathetic activity (high band of heart rate frequency variability analysis), peripheral sympathetic activity (pulse wave amplitude) and central arousal (number of spontaneous skin conductance responses). Also, we examined whether differences in psychophysiological reactivity can be correlated with self-ratings of psychological state and trait variables.

Methods

Subjects and Procedure

Fifteen patients with AD (2 male, 13 female; age range 14–55 years, mean age 27.7 years) and 15 healthy control subjects, matched for age, sex and educational level, participated in the study after having given their informed consent. All patients were inpatients at the Charité University Medicine Berlin, Campus Benjamin Franklin, and fulfilled the criteria of Hanifin and Rajka [1]. The severity of AD was evaluated by a scoring system modeled after the SCORAD [24] with 5 criteria studied (erythema, edema/pustules, dryness/crusts, excoriation, lichenification) rated for their intensity as (0) absent, (1) mild, (2) moderate or (3) severe. The intensity point values were added for each of the 5 criteria and severity defined as mild (1–5 points), moderate (6–10 points) and severe (11–15 points). The participants neither had cardiovascular or other chronic diseases nor received medication affecting the cardiovascular or nervous system. The first psychophysiological test was carried out shortly after admission to the hospital during acute exacerbation and was repeated during remission of AD, on average after 39 days. Testing of control subjects was performed with the same time interval between first and second examinations as for patients, to control for habituation to the experimental setting.

Study Protocol

Subjects were seated comfortably in a quiet room with an ambient temperature of 20–25°C. They completed a set of standardized German versions of psychological state and trait questionnaires. For time-stable variables, the trait anxiety scale (STAI-G Form X2) of Spielberger et al. [25] and the Beck depression inventory [26] were used. The acute psychological status was measured using the adjective word list EWL 60-S [27]. The EWL consists of 6 mood-rating scales, of which we chose to measure efficiency, general inactivation and emotional excitability for our study. The electrodes and transducers for detection of physiological parameters were then fastened to each subject's chest and nondominant arm and hand, and continuous recordings were made as follows. Heart rate and heart frequency variability were registered continuously by electrocardiography. The respiratory rate was registered through a piezo transducer (ATA-20 100; ZAK, Simbach am Inn, Germany) attached to the chest. The pulse wave amplitude was assessed by using a photoplethysmographic device (PLA-20100, ZAK) attached to the index finger. Systolic and diastolic blood pressures were registered continuously by using a Finapres device (Ohmeda, Louisville, Colo., USA) attached to the middle finger. The skin conductance level and the number of spontaneous skin conductance responses was measured using two Ag/AgCl electrodes (Hellige, Freiburg, Germany) attached to the thenar eminence of the palm.

Mental stress was induced using a standardized computer program [28]. In this program, an initial 5-min relaxation phase (prebaseline) was followed by a first stress phase, the manometer test, consisting of an information-processing task performed under time pressure (described in [29]), lasting approximately 7 min. The manometer test was followed by a second stress induction, the matrix test, which lacks the time pressure but includes a problem-solving task [30]. Recordings were made during the first 5 min of the manometer and matrix test. The two stress tests were followed by a second 5-min relaxation phase (postbaseline). The program was concluded by a final 5-min period of controlled respiration at 0.3 Hz. This phase controls for artifacts in the spectral analysis de-

Table 1. Heart rate, heart rate variability (high band), spontaneous skin conductance responses (SSCR) and pulse volume amplitude (PVA) in AD patients and controls (C) performing mental stress tests

	Heart rate, beats/min			High band, lnSMI			SSCR			PVA, units		
	AD	C	s	AD	C	s	AD	C	s	AD	C	s
1st examination												
Prebaseline phase	76.98 ± 8.43	72.64 ± 8.89		6.67 ± 1.21	7.22 ± 1.14		2.56 ± 2.92	3.21 ± 3.25		788.55 ± 790.11	872.10 ± 669.11	
Manometer test	80.43 ± 8.0	78.66 ± 10.2		6.39 ± 0.98	6.61 ± 1.04		7.43 ± 5.15	9.95 ± 4.33		766.09 ± 728.99	763.52 ± 641.51	
Matrix test	78.66 ± 8.41	75.48 ± 9.06		6.64 ± 0.93	6.89 ± 0.98		4.88 ± 3.60	6.45 ± 3.11		686.67 ± 676.77	642.04 ± 664.26	
Postbaseline phase	77.53 ± 7.87	72.00 ± 8.97		6.71 ± 1.01	7.16 ± 1.12		1.95 ± 2.20	4.00 ± 3.18	(*)	629.55 ± 671.51	547.79 ± 562.03	
Controlled respiration	76.54 ± 8.82	71.80 ± 8.84		6.52 ± 0.80	7.29 ± 1.33	*	2.03 ± 2.58	3.45 ± 3.24		583.83 ± 610.81	543.48 ± 547.31	
2nd examination												
Prebaseline phase	81.52 ± 6.59	73.70 ± 6.75	**	6.60 ± 0.65	7.15 ± 1.19		2.16 ± 2.81	4.59 ± 3.08	*	1134.4 ± 938.40	992.09 ± 652.89	
Manometer test	81.23 ± 8.49	77.64 ± 10.18		6.38 ± 0.65	6.74 ± 1.22		5.76 ± 5.36	11.89 ± 5.71	**	866.54 ± 647.31	881.89 ± 603.42	
Matrix test	80.16 ± 5.98	74.86 ± 8.27		6.55 ± 0.61	7.03 ± 1.12		3.09 ± 3.30	6.87 ± 3.07	**	844.73 ± 817.23	769.95 ± 574.75	
Postbaseline phase	79.25 ± 5.48	72.89 ± 7.59	*	6.69 ± 0.73	7.27 ± 1.37		2.55 ± 2.53	3.91 ± 2.97		820.26 ± 875.08	741.69 ± 608.80	
Controlled respiration	77.45 ± 7.16	72.17 ± 7.65	(*)	6.20 ± 0.96	7.13 ± 1.33	*	1.97 ± 2.42	2.59 ± 2.70		598.92 ± 751.55	756.41 ± 549.12	

All values are presented as means ± standard deviation. s = Significance, with ** $p < 0.01$, * $p < 0.05$, (*) $p < 0.1$ (group comparison; 2-tailed Mann-Whitney U test); lnSMI = natural logarithm of the squared modulation index.

scribed below. Following the period of controlled respiration, the subjects again completed the EWL questionnaire in order to judge their emotional response to the test.

Data Analysis and Statistics

The skin conductance level was recorded on a polygraph (Uniscript UD 210, Schwarzer, Munich, Germany) and the number of spontaneous responses was analyzed manually. All other physiological parameters were recorded online (EasyLab, version 6.1, Stemmer PC systems, Puchheim, Germany) and analyzed by ALYS software (version 1.18, T. Sudhop and H. Schaechinger, Basel, Switzerland). Median values for each subject for each of the five 5-min periods recorded were analyzed under visual artifact control. The power spectral density of the heart rate was analyzed by Fourier transformation with the Carspan software package (version 1.2., Mulder, Groningen, the Netherlands). We corrected for variations in baseline heart rate by calculating the squared modulation index (SMI). The low, middle and high bands were defined as 0.02–0.06, 0.07–0.14 and 0.15–0.4, respectively.

Statistical analysis was performed by SPSS+ (SPSS Inc., Chicago, Ill., USA). All values are expressed as means ± standard deviation (SD). We used two nonparametric tests, the Mann-Whitney U test for unpaired samples to compare patients with controls and the Wilcoxon test for paired samples to compare active and inactive phases of the disease. Mean values were considered to be significantly different when $p \leq 0.05$.

Results

Patient Data

The age of the AD patients ranged from 14 to 55 years (mean 27.7), of the control group from 13 to 54 years (mean 26.5). Thirteen patients and 13 controls were female, 2 in each group were male. They were matched for educational level (years of school attended and degree obtained). At the time of the first psychophysiological test, 9 patients had moderate and 6 had severe AD lesions, while they were mild in all 15 patients upon reexamination. Patients were asked to evaluate the perceived influence of genetics, environmental factors and psychological stress on manifestation and course of their disease on a scale from 0 (none) to 5 (very strong). They perceived psychological factors as the strongest influence (3.69 ± 1.11), followed by environmental (3.08 ± 1.12) and genetic factors (2.25 ± 1.49).

Heart Rate

To determine differences in the β-adrenergic activity of the sympathetic nervous system between AD patients and controls, we measured their heart rate in response to mental stress (fig. 1a, table 1). In the first examination, both groups did not differ significantly in their heart rate over time or in response to a mental stimulus. Nevertheless, the mean heart rate was consistently higher in AD patients versus controls (table 1). Unexpectedly, the increase in heart rate in response to a mental stimulus was higher in controls than in AD patients, albeit not significantly (6.01 ± 6.8 and 3.45 ± 4.9 beats/min, respectively; table 2). In the second examination, with AD patients being in remission, their heart rate was significantly higher than that of the controls in prebaseline (AD patients 81.5 ± 6.59 beats/min, controls 73.70 ± 6.75 beats/min; $p < 0.01$) and postbaseline phases (AD patients 79.25 ±

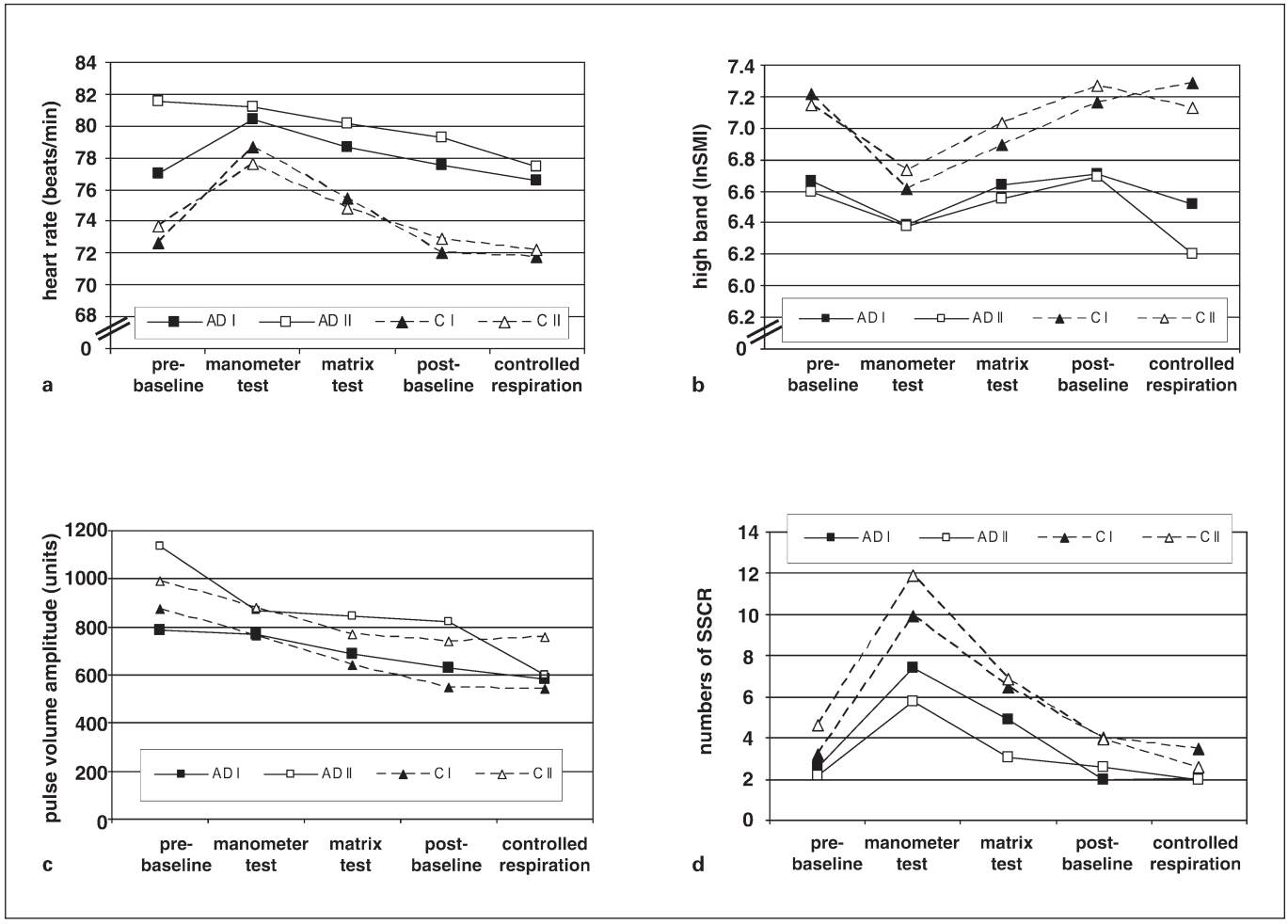

Fig. 1. Heart rate (**a**), high band of heart rate variability (**b**), pulse volume amplitude (**c**) and number of spontaneous skin conductance responses (SSCR, **d**) in AD patients and controls in resting phases (prebaseline and postbaseline), under mental stress (manometer test and matrix test) and under controlled respiration. AD I = AD patients, 1st examination; AD II = AD patients, 2nd examination; C I = controls, 1st examination; C II = controls, 2nd examination; lnSMI = natural logarithm of the squared modulation index.

5.48 beats/min, controls 72.89 ± 7.59 beats/min; $p < 0.05$). Again, the increase in heart rate in response to stress was higher in the control group (+3.94 ± 6.6 beats/min), while it even decreased in AD patients (–0.29 ± 1.1 beats/min; $p < 0.01$).

High-Frequency Fluctuations of Heart Rate Variability

The spectral analysis of heart rate variability is a valid instrument to quantify the activity of the autonomic nervous system [31]. Rhythmic fluctuations of heart rate variability were analyzed at frequencies from 0.01 to 0.5 Hz. Heart rate variability at high and medium frequencies (high and mid band) reflects modifications in parasympathetic activation, while low frequencies are affected by the sympathetic as well as the parasympathetic nervous system [32]. High rate fluctuations >0.15 Hz are predominantly vagal [33]. Thus, we used the high band of the spectral analysis of heart rate variability as a measure of parasympathetic activity. Figure 1b shows that, regardless of disease activity, AD patients had consistently lower values than the controls. This difference was significant under controlled respiration in both the first and the second examinations (AD patients 6.52 ± 0.80 and 6.20 ± 0.96 lnSMI, respectively, vs. controls 7.29 ± 1.33 and 7.13 ± 1.33 lnSMI, respectively) (table 1). While the high band decreased in both groups upon administration

Table 2. Differences in heart rate, heart rate variability (high band), spontaneous skin conductance responses (SSCR) and pulse volume amplitude (PVA) between prebaseline phase and manometer test in AD patients and controls

	AD	Controls	s
Heart rate, beats/min			
1st examination	3.45 ± 4.9	6.01 ± 6.80	
2nd examination	–0.29 ± 1.1	3.94 ± 6.6	(*) 0.051
High band, lnSMI			
1st examination	–0.28 ± 0.6	–0.6 ± 0.9	
2nd examination	–0.22 ± 0.4	–0.41 ± 0.7	
SSCR			
1st examination	4.78 ± 4.22	6.73 ± 3.31	
2nd examination	3.60 ± 3.76	7.31 ± 4.36	*
PVA, units			
1st examination	–22.46 ± 185.89	–108.58 ± 184.93	
2nd examination	–267.87 ± 119.18	–119.19 ± 309.53	

All values are presented as means ± standard deviation. s = Significance, with * $p < 0.05$, (*) $p < 0.1$ (group comparison; 2-tailed Mann-Whitney U test); lnSMI = natural logarithm of the squared modulation index.

Table 3. Psychological state variables in AD patients and controls before and after the mental stress test (EWL 60-S mood-rating scales for emotional excitability, inactivation and efficiency)

	AD	Controls	s
1st examination			
Emotional excitability			
Before stress	3.93 ± 1.8	1.60 ± 1.4	**
After stress	3.73 ± 1.9	1.80 ± 1.1	**
Inactivation			
Before stress	3.93 ± 2.8	2.00 ± 1.7	(*)
After stress	3.73 ± 2.8	1.53 ± 1.8	**
Efficiency			
Before stress	4.27 ± 2.7	5.33 ± 1.9	
After stress	4.40 ± 2.6	4.73 ± 2.0	
2nd examination			
Emotional excitability			
Before stress	3.31 ± 1.9	1.33 ± 1.3	**
After stress	3.33 ± 2.3	1.73 ± 1.4	(*)
Inactivation			
Before stress	1.77 ± 1.7	1.20 ± 1.7	
After stress	2.07 ± 1.7	1.80 ± 1.7	
Efficiency			
Before stress	5.23 ± 1.9	4.73 ± 1.9	
After stress	4.53 ± 2.7	4.67 ± 1.7	

All values are presented as means ± standard deviation. s = Significance, with ** $p < 0.01$, (*) $p < 0.1$ (group comparison; 2-tailed Mann-Whitney U test).

of the first stressor, there was no significant difference between patients and controls (table 2).

Pulse Volume Amplitude

Since peripheral vasoconstriction is regulated solely by α-adrenergic fibers, the pulse volume amplitude served as a measure for α-adrenergic sympathetic activity. Peripheral vasoconstriction was higher in the first than in the second examination in both groups. As expected, the pulse volume amplitude fell in both groups upon stimulation (baseline versus manometer), but there were no significant differences between patients and controls (table 2, fig. 1c). Interestingly, the pulse volume amplitude did not recover after cessation of the stressor or under controlled respiration (table 1). The peripheral vasoconstriction showed strong interindividual differences, leading to a high SD. The intraindividual values were relatively stable around a given level so that the mean values are comparable.

Electrodermal Activity

The number of spontaneous skin conductance responses under mental stress is widely seen as a measure for central arousal [34]. We hypothesized that the mental stress induced by the manometer and matrix test would lead to higher spontaneous fluctuations in the AD group. On the contrary, the controls showed a higher number throughout both examination periods (table 1, fig. 1d). Interestingly, the control group reacted even more strongly in the second examination, showing no habituation effect. While the number of spontaneous skin conductance responses increased from the prebaseline to the manometer test in both groups, this increase was significantly higher in the control group in the second examination as compared to the AD patients.

Psychological Tests

In accordance with previous studies [5, 6, 21], AD patients had significantly higher measures of trait anxiety (STAI-G; AD patients 48.07 ± 8.37 vs. controls 37 ± 6.51, $p < 0.01$) and depression (Beck depression inventory; AD patients 18.87 ± 11.43 vs. controls 5.33 ± 3.59, $p < 0.01$). Both anxiety and depression fell in the pathological range of the psychological inventories. The analysis of the time-sensitive mood-rating instrument EWL [27] resulted in interesting additional information. In the

self-ratings for emotional excitability, the AD patients ranked themselves consistently and significantly higher than controls (table 3), regardless of their symptoms. In the active phase of their disease, AD patients evaluated their level of general inactivation significantly higher than control subjects, while there was no significant difference in remission. There were no statistically significant differences in self-ratings between patients and controls or between phases of disease activity.

Discussion

We were unable to confirm our hypothesis that AD patients display a higher psychophysiological reactivity in response to mental stress than healthy controls. AD patients did not react more strongly to a mental stressor than the controls as measured by heart rate, high-frequency fluctuations of heart rate variability, electrodermal activity or pulse volume amplitude. Nevertheless, we did see evidence for a higher activational level in AD regardless of disease activity.

AD patients had a higher heart rate (i.e. higher sympathetic activity) and a lower high band of heart rate variability analysis (i.e. lower parasympathetic activity) than the control group throughout the entire test, consistent with findings by Langewitz et al. [33] who described vagal inhibition as a physiological answer to increased sympathetic activity. While the control group had a very similar reaction pattern at both time points, the AD group had a significantly elevated heart rate in the pre- and postbaseline phases of the second examination.

It is possible that this reflects a certain sympathetic overactivation in AD that may have made it difficult for patients to find resting conditions that would allow for further increases in activation in response to mental stress.

The pulse volume amplitude, recorded as a measure of the α-adrenergic component of the sympathetic nervous system, decreased in both groups upon mental stress, but we did not see significant differences between the two groups. The pulse volume amplitude is a sensitive marker of peripheral activation. Slight changes in activation lead to marked changes in peripheral blood supply. Likewise, cooling of the limbs will lead to decreased blood supply due to vasoconstriction [35]. We performed this study under ambient temperature, but we cannot exclude the possibility that the prolonged physical inactivity, necessary to perform the computer-based test, led to the increased peripheral vasoconstriction observed over time.

Although the increased sympathetic arousal in AD patients might be expected to translate to increased skin conductance responses, usually seen as a marker for central arousal, we did not see such an effect in our patient group. In contrast, the control group displayed significantly higher levels and responses to mental stress than the AD patients. This is consistent with the findings of Koehler and Weber [23], who found lower skin conductance levels and responses in 20 AD patients compared to 20 healthy controls. A possible reason may be the dryness (xerosis) of the skin, indicative of the disease. The moisture content of the upper skin layers plays a major part in developing skin conductance, and an increased transepidermal water loss, as seen in AD patients [36], may lead to lower levels in skin conductance. Thus, an interpretation of this parameter has to be done cautiously in AD.

Despite the lack of data indicating higher psychophysiological reactivity in AD patients, our findings support earlier studies showing generally higher sympathetic activation levels in AD when measured by heart rate. Faulstich et al. [21] examined 10 patients in acute exacerbation and compared them to 10 healthy controls. The heart rate increased in both groups under pressure, but only the control group showed a significant reduction in the cold-pressure test, indicating increased arousal in AD. Munzel and Schandry [22] found parallel increases in heart rate in AD patients and controls, although patients showed a higher response to mental arithmetic. Again, they lacked a general deactivation. The mere mention of increasingly difficult mental arithmetic prompted AD patients to increase their heart rate, while it fell in the control group. The findings of these older studies support our notion that heightened arousal in anticipation of a stressor may prevent an increased stress reactivity. Interestingly, patients often report a decreased ability to relax [37]. This was also the case in our study, in which the patients reported agitation and preoccupation with personal problems in the resting phases (data not shown).

In regard to the psychological profile of AD patients, our study confirms previous observations showing that AD patients have highly increased levels of both anxiety and depression [5, 6, 21]. Anxiety disorders are typically accompanied by persistent sympathetic overarousal [38], and, thus, increased anxiety levels in AD could lead to the sympathetic predominance seen in our study. Nevertheless, chronically ill patients may react with increased anxiety and depression to the chronicity of their disease, regardless of diagnosis. In earlier studies by Garrie et al. [39] and Ginsburg et al. [6] however, anxiety in AD pa-

tients was significantly higher compared to patients with an acute self-limiting skin disease (pityriasis rosea) or a chronic skin disease (psoriasis). Thus, it is unlikely that anxiety in AD, as seen in our study and by others, is just a result of the burden of having an acute or chronic skin disease. While anxiety and depression as constant trait variables have been studied in AD, it has not been attempted thus far to correlate psychological state variables, which are subjective and situation dependent, with different phases of the disease. Our finding that AD patients rate themselves more inactive when having acute symptoms fits the physiological finding of a lower baseline activity in terms of heart rate in the acute phase. We generally find an increased emotional excitability in AD patients regardless of disease phase and regardless of whether they are expecting a mental task or have already performed it. These findings confirm an earlier study by Gieler et al. [5] who found AD patients to be more anxious and aroused but less energetic. We show that the high level of emotional excitability is a stable psychological characteristic in AD that is independent of acute influences. Nevertheless, whether the psychophysiological characteristics of AD patients seen in this and other studies predate the manifestation of their disease or are a consequence of their chronic skin condition remains to be explored.

The lack of statistically significant differences in the stress response may be due to our limited sample size and, thus, limited statistical power. Another possible confounding factor may be gender, since it has recently been shown that a subgroup of female AD patients experiences premenstrual skin worsening in addition to the symptoms of premenstrual syndrome [7]. Thus, the interpretation of physiological, pharmacological and psychological studies of autonomic abnormalities in AD is rendered difficult by the complexity of mechanisms that maintain homeostasis, and further studies on isolated aspects of the disease will be needed to clarify its pathogenesis. Nevertheless, AD patients seem to have a higher activation level, physiologically as well as psychologically, further emphasizing that the use of psychotherapeutic intervention [40], even in disease-free intervals, in addition to the necessary dermatological treatment may be beneficial.

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