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INVESTIGATIVE REPORT

Effect of Itch, Scratching and Mental Stress on Autonomic Nervous System Function in Atopic Dermatitis

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Atopic dermatitis is a stress-responsive disorder that involves the autonomic nervous system. The current study used heart rate variability to examine the effect of itch, scratching and mental stress in atopic patients with moderate to severe disease. Twenty-one patients with active disease and 24 healthy volunteers participated in the study. Heart rate variability measurements were taken at 5 min intervals at rest and after each of 3 acute stress tests, which included histamine-induced itch at the forearm, scratching around the itch site, and the Trier Social Stress Test. Atopic patients displayed a higher heart rate than healthy controls in all 4 experimental settings, which was statistically significant using Cohen's delta analysis. The very low frequency component of the power spectrum, indicative of sympathetic activity, showed a 200% increase after scratching in patients with atopic dermatitis. The high frequency component, reflecting parasympathetic tone, responded swiftly to itch and scratching in healthy controls, but displayed a limited adaptability in atopic dermatitis. This study supports the concept that atopic dermatitis is a stress-responsive disorder and involves autonomic nervous system dysfunction. Atopic subjects exhibited an overactive sympathetic response to itch and scratching, while the parasympathetic tone was persistently and rigidly elevated, showing a lack of adaptability in response to stress. ***Key words: atopic dermatitis; heart rate variability; acute stress; autonomic nervous system; itch and scratching.***

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Atopic dermatitis (AD) is a pruritic inflammatory disease in which stress clearly exacerbates itch (1, 2). The disease worsens when patients are under stressful conditions involving hard work or conflicting human relationships (3). Patients feel severe itch and cannot refrain from scratching. Scratching worsens the dermatitis and creates more itch, resulting in a scratch-itch cycle that further perpetuates a high state of anxiety (4). Consequently, anxiety and active disease lead to a decline in the quality of life of patients with AD, which most notably includes their quality of sleep (1, 5). AD alters the immune response in the skin, damages barrier function, and contributes to systemic dysregulation of the homeostatic neural, endocrine and immunologic pathways (6–8).

The autonomic nervous system (ANS) has a major role in the stress response that subsequently results in the activation of fight or flight systems (9). Several studies suggest that dysfunction of the ANS may contribute to pruritus in patients with AD (10). Acetylcholine (ACh) has been implicated as a possible mediator of pruritus in patients with AD, intradermal injections of ACh being shown to elicit pruritus instead of pain in patients with AD, via a histamine-independent mechanism (11–13). Vagal nerve stimulation inhibits experimentally induced itch, probably by a central mechanism (14). Finally, sweating, which is under autonomic control, is often associated with pruritus in patients with AD (15). Studies have demonstrated that unmyelinated fibers controlling sudomotor activity are affected in AD (16).

Previous studies in patients with chronic disease have utilized heart rate variability (HRV) as a tool for monitoring ANS function (17, 18). HRV measures variations around beat-to-beat intervals of the heart rate, and the measurements translate into a set of parameters that reflect a state of sympathetic (stress, anxiety) or parasympathetic (relaxation, calmness) activation in the body (19, 20). Previous HRV studies in patients with AD have shown that this group has altered heart rate and dysfunctional vagal tone, even in the absence of acute stressors (21, 22). To date, no studies have addressed ANS function under conditions that mimic the itch-scratch cycle.

The primary aim of the current study was to examine the effect of itch, scratching and psychological stress on the ANS response in patients with AD who have moderate to severe disease in comparison with healthy volunteers. HRV parameters were utilized as measures of ANS activity. A second aim was to assess whether acute itch, scratching and psychological stress affects

sweating, trans-epidermal water loss (TEWL) and skin moisture differently in patients with AD.

MATERIALS AND METHODS

Participants

Twenty-one subjects with active AD and 24 healthy controls between the ages of 18 and 50 years with similar age and ethnicity participated in the study. Subjects with heart disease, hypertension, diabetes, or a history of psychiatric disease were excluded from the study. Subjects were also excluded if they consumed 4 or more caffeinated beverages daily or were taking medications such as beta-receptor antagonists, calcium channel antagonists, vasodilators, oral antihistamines, or any psychotropic drugs. Caffeine consumption was not permitted on the day of the experiment. The subjects with AD were diagnosed by the criteria of Hanifin & Rajka and had clinical findings compatible with moderate to severe AD based on an investigator's global assessment score (IGA) (23). All participants provided written informed consent and were free to withdraw from the study at any time. All procedures were approved by the Institutional Review Board of Wake Forest University Health Sciences.

Data collection

Measurement of HRV and R-R intervals were performed using a non-invasive plethysmographic sensor (Pulse Wave Sensor, HRM-02, Biocom Technologies, Bellevue, WA, USA). The probe was placed on the left earlobe and HRV was continuously recorded during each 5-min assessment period. Beat-to-beat heart rate (HR) was recorded using Biocom Technologies "HRV Live!" software and photoplethysmography technology (Biocom Technologies) (24). Measurements were taken at 5 min intervals (25). This technique provided information about sympathetic and parasympathetic activity.

Experiment outline

Tests and measurements were performed in the order outlined in Fig. 1. The experiment was performed in the morning before 12.00 am for all patients. All measurements were taken in a controlled room environment at 21ºC after an initial acclimatization of 20 min. There was an interval of at least 10 min between each stress test. HRV recordings were taken in 5 min segments. Subjects were instructed to sit comfortably and breathe normally. They were not allowed to speak during the HRV recordings.

Histamine iontophoresis

Itch was evoked using a round iontophoresis electrode 14 mm in diameter on an involved dorsal or ventral forearm site of AD, with a corresponding site for healthy controls. For iontophoresis, a 1% solution of histamine was dissolved in a 2% methylcellulose gel (Sigma, St Louis, USA) and administered with a current of 200 μA for 30 s (Perimed PF3826 Perilont Power Device, Perimed, Stockholm, Sweden). Itch ratings were obtained using a numerical scale from 0 to 10, one min after the histamine stimulus was applied.

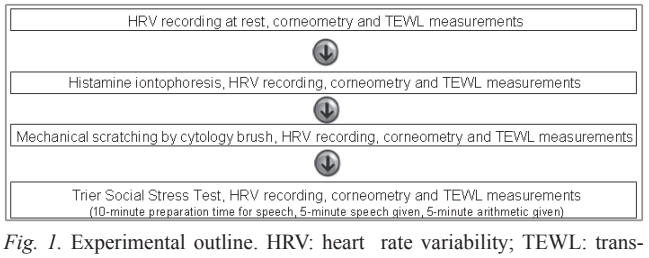

Fig. 1. Experimental outline. HRV: heart rate variability; TEWL: trans-epidermal water loss.

Scratching

Subjects underwent artificial scratching over the area for the forearm 3 cm distal to the edge of the area of histamine iontophoresis for 2 min. Scratching was accomplished by study personnel repetitively moving a cytology brush (Medi-Pak 7-inch cytology brush, 24-2199, General Medical Corporation, Elkridge, MD, USA) over the ventral forearm. Uniformity was controlled by applying sufficient pressure to bend skin-facing brush bristles so that the brush handle touched the skin surface, as described previously (26). The same member of the research team applied the cytology brush for all subjects. Itch ratings were obtained using a numerical scale from 0 to 10, one min after the scratching stimulus was applied.

Trier Social Stress Test

Trier Social Stress Test (TSST) (27) involved a 5 min public speech followed by 5 min of a mental arithmetic test performed before an evaluative panel of two people. The task aimed to produce moderate increases in cortisol, heart rate and blood pressure, as well as subjective reports of anxiety in healthy individuals (28, 29). The instructions stated that the participant had to give a 5 min speech to interviewers. The subjects were given 10 min to prepare their speech prior to the TSST. In the examination room, two interviewers sat behind a computer equipped with the camera. Study subjects sat approximately 2 m in front of the interviewers and video camera and were able to see themselves on a monitor throughout. Participants were instructed to begin their speech. After 5 min, they were instructed to begin a serial subtraction task that lasted for 5 min. The total duration of the test was 10–15 min for all participants. Although participants believed that they were being filmed, no actual recording took place. The purpose of this was merely to increase stress levels within the subjects.

Corneometry and trans-epidermal water loss measurements

Skin hydration was assessed after each session of HRV measurements using non-invasive corneometry (Delfin Technologies Ltd, MoistureMeter SC-2, Kuopio, Finland). The MoistureMeter is a sensitive corneometry device that determines the capacitance of the stratum corneum and reflects the relative moisture level in the stratum corneum (30). Two measurements were taken from the closest unaffected AD site on the same forearm as iontophoresis and scratching. The remaining two measurements were taken on the palm of the same arm. Each measurement took about 15 s.

TEWL was measured using a Delfin™ VapoMeter (Delfin Technologies Ltd, VapoMeter SWL3N, Kuopio, Finland) after each session of HRV measurements. The measurement of TEWL is a non-invasive method that utilizes a closed chamber. The device consists of hydrosensors coupled with thermometers that measure the rate of evaporation at two distances from the skin surface. TEWL is calculated from the slope provided by the two sensors, and TEWL values were registered in $g/m^2/h$. Two measurements were taken from the closest unaffected AD site on the same forearm as iontophoresis and scratching. The remaining two measurements were taken on the palm of the same hand.

Analysis of heart rate variability

Physiological interpretation of HRV parameters are summarized in Table I. All HRV parameters were calculated on "normal-to-normal" (NN) interbeat intervals caused by normal

Table I. *Physiological interpretation of heart rate variability (HRV) parameters*

HRV parameter	Significance
HRT (heart rate)	Sympathetic/parasympathetic balance
SDNN (standard deviation of normal R-R intervals)	Degree of autonomic regulation
RMSSD (root mean square of successive differences)	Parasympathetic tone
TP (total power of the HRV spectrum)	Total strength of autonomic nervous system
VLF (very low frequency component of power spectrum)	Sympathetic regulation
LF (low frequency component of power spectrum)	Sympathetic/parasympathetic balance and cardiorespiratory coherence
HF (high frequency component of power spectrum)	Parasympathetic tone
LF:HF ratio	Sympathetic/parasympathetic balance

heart contractions paced by sinus node depolarization (25). All time-domain parameters were derived directly from NN intervals recorded during the study. Time-domain indexes were as follows: the average R-R interval value (heart rate), the standard deviation of normal to normal beats (SDNN), and the root mean squared of the standard deviation (RMSSD). Higher SDNN and RMSSD values are known to be associated with a well-controlled autonomic regulation and better health (25).

In the frequency domain, power spectral analysis was performed using a Fast Fourier Transform (FFT) algorithm. The computer software used this algorithm to define the power spectral density (31). The data were normalized by dividing the power of a given component from the total power. Within the spectrum, the high-frequency component (HF) (0.15–0.50 Hz) is an indicator of parasympathetic tone, the low-frequency component (LF) (0.04–0.15 Hz) is a measure of sympathetic/parasympathetic balance, and the very low-frequency component (VLF) (0.003–0.04 Hz) is an indicator of sympathetic regulation (25, 32–33).

Statistical analysis

Statistical power for this study was established on the whole sample size and based on the specific contrast of the pre- vs. post-change between either of the control groups. NQuery 5.0 was used to derive the sample size. This prediction was based on a pilot study on differences in HRV. Based on a two-group Satterthwaite *t*-test of equal means (unequal variances) (equal Ns) a sample size of 20 per group results in 80% power to detect those size differences low/high frequency ratio (m = 1.39 ± 0.83 m = 1.3 ± 0.63 alpha = 0.05, two-sided).

Repeated measures analysis of variance (ANOVA), or mixed linear models were used to assess the effect of the 3 conditions and to delineate confounders (e.g. sex, age). Descriptive statistics were used to summarize baseline demographics. Data was collected, coded and entered into SPSS v.16 software for analysis. Within the healthy control group, comparisons were made between baseline and each state induced by 3 acute stressors. The same comparisons were made within the AD group. Comparisons were also made between control and AD at baseline and then in each post-stress setting, and reported using *p*-values when less than 0.05, as well as Cohen's delta to demonstrate large changes that approached statistical significance.

Cohen's delta or *d* is a measure of effect size or the standard mean difference (34). Cohen's *d* is a standard measure used to calculate treatment effect and describes differences in means relative to an assumed common variance. According to Cohen, effect size changes can be classified as: small (0.20); medium (0.50); and large (0.80). In this study, Cohen's *d* was used to show large changes otherwise not detected due to large variances.

RESULTS

The study included 21 atopic patients with active disease (6 males and 15 females) and 24 healthy volunteers (12 males and 12 females). Patients with AD had a mean age of 31.8 ± 9.0 years (range 18–47 years). Healthy controls had a mean age of 28.9 ± 7.6 years (range 19–42 years). The mean ages of the AD and control groups were not statistically different. There were more females than males in the AD group, but ANOVA analysis showed that gender was not a confounding factor in the control or AD group. Patients with AD had a significantly higher histamine-induced itch rating of 4.3 out of 10, compared with 2.6 out of 10 for healthy controls ($p = 0.004$). The AD group was homogenous with regards to disease severity (23 patients with moderate and 1 with severe disease).

Patients with atopic dermatitis present a higher heart rate than healthy controls

Heart rate across all 4 experimental settings showed that AD had a higher heart rate than healthy controls (Fig. 2). Using Cohen's delta test to statistically equalize differences between the two groups, a large difference in heart rate was noted in all parameters (Cohen's $d > 0.8$ at rest, post-histamine, post-scratching and post-stress).

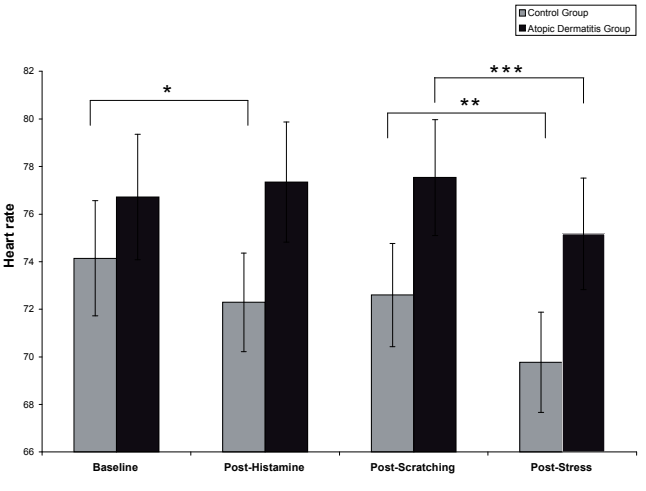

Fig. 2. Heart rate (in beats per min) in the atopic dermatitis (AD) group compared with the control group in all 4 experimental settings. *Significant differences in the control post-histamine group vs. control baseline (*p* is set at 0.05); **relevant difference in the control post-scratching group vs. control post-stress; ***relevant difference in the AD post-scratching group vs. AD post-stress. Control *n* = 24, AD *n* = 21.

Healthy controls experienced a significant decrease in heart rate from rest after histamine-induced itch ($p = 0.006$) and another significant decrease in heart rate from post-scratching to post-stress ($p = 0.001$). Patients with AD experienced a significant decrease in heart rate from post-scratching to post-stress ($p = 0.01$).

Patients with atopic dermatitis have a more robust sympathetic response to itch and scratching than controls, as depicted by very low-frequency and low-frequency values

In patients with AD, the 3 stressors induced an increase in VLF from baseline, which was statistically significant after histamine-induced itch ($p = 0.02$) and notable after scratching ($p = 0.07$) and psychological stress ($p = 0.08$). In healthy controls, the 3 stressors induced an increase in VLF compared with baseline (Fig. 3), which was statistically significant only after psychological stress ($p = 0.02$).

In the AD group, scratching induced a 200% increase in the magnitude of VLF and a 100% increase in the magnitude of LF from baseline (Figs. 3–4). Three patients with AD had very high values for VLF and LF after scratching, and when the subjects were taken out of the analysis the VLF value remained elevated from baseline.

Cohen's delta analysis on VLF and LF showed a large difference between the AD group and healthy controls after histamine-induced itch and scratching (Cohen's $d > 0.8$ for post-histamine and post-scratching).

Patients with atopic dermatitis present a dysfunctional parasympatethic response to itch and scratching, as depicted by high-frequency component values

In healthy volunteers, HF increases rapidly after itch is induced by histamine and then promptly decreases after scratching. In comparison, the atopic group presented an elevated HF at rest, which remained elevated when exposed to acute stressors, displaying a limited fluctuation in a narrow band (Fig. 5).

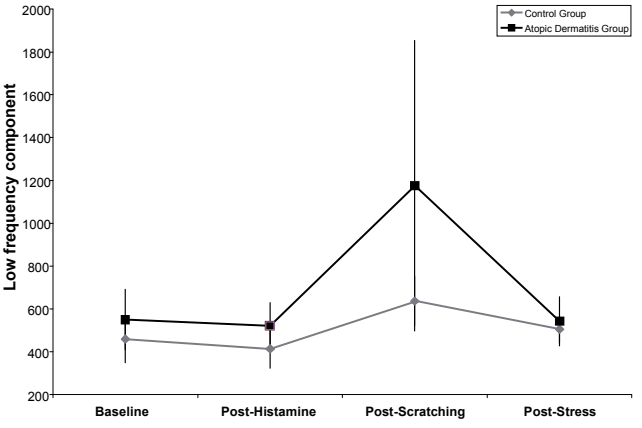

Fig. 4. Effect of histamine-induced itch, scratching and psychological stress on the low frequency (LF) component of the heart rate variability spectrum (mean ± SEM). Scratching induces a 100% increase of LF from baseline in the atopic group.

Patients with atopic dermatitis have lower skin hydration and higher trans-epidermal water loss than controls

Skin hydration was lower and TEWL was higher on the forearms and palms of patients with AD compared with controls (Table II). This difference was statistically significant at rest in forearm corneometry ($p < 0.05$) and significant after histamine-induced itch and psychological stress in forearm TEWL ($p = 0.003$, 0.007 respectively).

Interestingly, acute stressors affected the corneometry and TEWL values in the palm of both the control and the AD group. There was a significant decrease from rest in palm corneometry after histamine-induced itch and

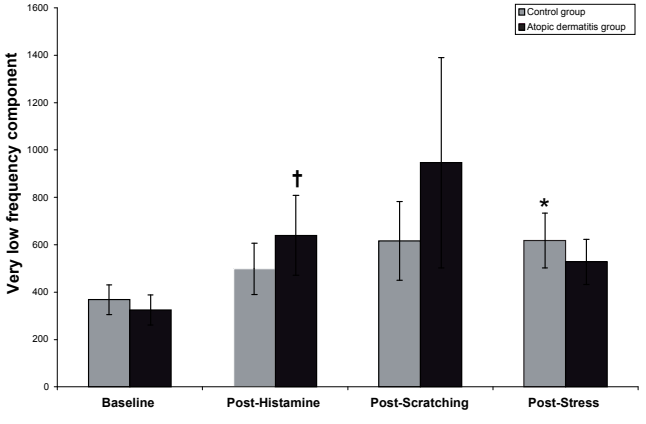

Fig. 3. Effect of histamine-induced itch, scratching and psychological stress on the very low frequency (VLF) component of the heart rate variability spectrum (mean ± SEM). *Significant differences in the control group vs. control baseline values; †relevant difference in the atopic group vs. atopic baseline values.

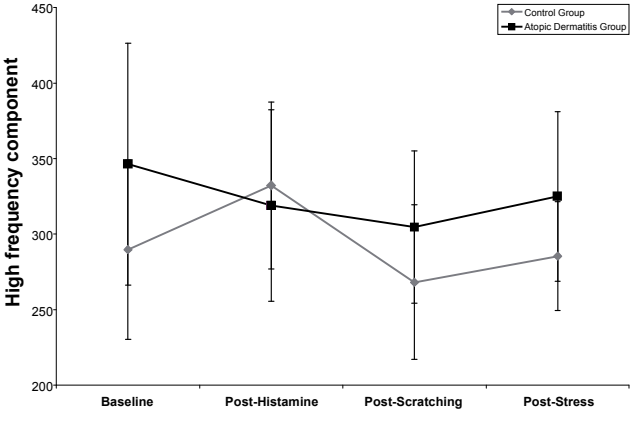

Fig. 5. Effect of histamine-induced itch, scratching and psychological stress on the high frequency (HF) component of the heart rate variability spectrum (mean ± SEM). HF values in the control group fluctuate in response to histamine and scratching, while HF values in the atopic dermatitis (AD) group remain persistently elevated at rest and during acute stress.

Table II. *Skin hydration and trans-epidermal water loss (TEWL) values following histamine-induced itch, scratching and psychological stress in the forearm and palm. *Significant differences in the control group vs. control baseline values; †relevant difference in the atopic group vs. atopic baseline values; ‡values in the atopic group are different compared with healthy control values for the same stimulus (*p *= 0.05). Control* n = *24, atopic dermatitis (AD)* n = *21*

	Baseline		Histamine		Scratching		Social stress	
Heart rate variability parameters	Control	AD	Control	AD	Control	AD	Control	AD
Forearm corneometry	22	16.5	19.5	14	19.6	12.9	20.8	15.7‡
Palm corneometry	53.6	41.7	36.6*	33.5	29.2*	23.2	50.5	37.3
Forearm TEWL	8.58	10.6	7.03	10.6‡	9.51	10.8	7.25	11.5‡
Palm TEWL	71.3	76	51.9*	55.4†	47.3*	54.3†	55.1*	67.4

*Significant differences in the control group vs. control baseline values; †relevant difference in the atopic group vs. atopic baseline values; ‡values in the atopic group are different compared with healthy control values for the same stimulus ($p = 0.05$).

scratching in healthy controls ($p = 0.012$, $p = 0.007$ vs. resting values, respectively) and a significant decrease in palm TEWL after histamine, scratching and stress in healthy controls ($p = 0.004$, < 0.001, 0.006, respectively). Patients with AD had a significant decrease from rest in palm TEWL after exposure to histamine and scratching ($p = 0.004$, 0.002).

Overview

All of the HRV parameters are presented in Table III. In both the control and AD group, SDNN and RMSSD increased in response to all 3 acute stressors, and the response reached statistical significance for SDNN in the control group and AD group after psychological stress ($p = 0.006$, $p = 0.03$, respectively).

DISCUSSION

The present study used spectral analysis of HRV to explore the response of the ANS to acute itch, scratching, and mental stress in AD patients. Patients with AD exhibited a sympathetic overactivation, as reflected by an elevated heart rate in all experimental settings and an increased VLF after itching and scratching. These findings are in agreement with a previous report that showed that heart rate is consistently elevated in AD, even in the absence of acute stress (22). Similarly, heart rate was found to be elevated in patients with psoriasis, another stress-responsive disorder, irrespective of the presence of an acute stressor (35). In contrast, another HRV study found that patients with AD exhibit a lower heart rate at rest and explained it as a consequence of an increased vagal input (21). In this study, an elevated heart rate was a consistent finding. In the context of AD, the vicious itch-scratch cycle may be the cause that perpetuates stress and it has been reported that prolonged or unresolved stress may result in significantly elevated resting heart rate (36).

The 200% increase in VLF magnitude after scratching in atopic eczema patients suggests a significant sympathetic response that differs from healthy controls. Previous studies have shown that scratching in atopic eczema increases the intensity of histamine-induced itch, while in healthy subjects it inhibits itch (26, 37). Notably, there was a concomitant 100% increase in LF, which also suggests that there is an exaggerated sympathetic response in AD compared with healthy controls. Functional magnetic resonance imaging studies have shown that scratching normally inhibits the unpleasant emotions associated with itch via the anterior cingulate cortex (ACC), but activity in this area of the brain may be altered in AD (38, 39). The anterior portion of the ACC controls heart rate and the ANS during short-term modulation of HRV (40), and therefore it is conceivable that the present HRV data could provide a glimpse of the central effect of scratching in chronic itch.

In addition to sympathetic hyperactivity, the current study found a dysfunctional parasympathetic response

Table III. *Heart rate variability (HRV) parameters at rest and after histamine-induced itch, scratching and psychological stress. Control* n = *24, atopic dermatitis (AD)* n = *21*

	Baseline		Histamine		Scratching		Social stress	
HRV parameters	Control	AD	Control	AD	Control	AD	Control	AD
Heart rate	74.1	76.7	72.3*	77.4	72.6	77.5	69.8*	75.2
Standard deviation of beat-to-beat intervals	57.3	57.3	59.6	63.5	65.9	67.3	70.1*	68.0†
Root means squared of the standard deviation	49.2	49.5	51.2	53.6	54.6	55.7	55.8	58.1
Total power of the HRV spectrum	1116.4	1220.2	1243.7	1500.9	1520.2	2426.5	1407.4	1394.9
Very low frequency component of power spectrum	367.9	324.1	498	639.6†	615.5	946.5	617.9*	527.8
Low frequency component of power spectrum (LF)	458.9	549.7	413.4	520.8	636.6	1175.3	504.1	542.1
High frequency component of power spectrum (HF)	289.7	346.3	332.2	318.9	268.2	304.7	285.5	324.9
LF:HF	2.3	2.25	1.45*	1.72	3.8	2.64	2.18	1.99

*Significant differences in the control group vs. control baseline values; †relevant difference in the atopic group vs. atopic baseline values ($p = 0.05$).

to acute stress in AD. While the HF in healthy controls *increased* after induction of itch and promptly decreased after scratching, the HF in atopic patients fluctuated in a divergent pattern: slightly *decreasing* after itch and further decreasing in a limited measure after scratching, with all changes being confined to a narrow band (Fig. 5). This trend suggests an impaired response of the parasympathetic arm: the vagal tone in AD displays a certain rigidity, a limited ability to adapt to challenges such as those presented by exogenous itch and scratching. A recent study found an elevated RMSSD as evidence for a higher vagal tone in AD (21). In our study we found a slightly elevated RMSSD at rest in the AD group, and this parameter did not vary significantly during acute stress. The present HRV model found that the stress level induced by scratching is notably higher in atopic patients, consistent with the discomfort known from clinical observation. We also found evidence for an increased parasympathetic tone, which can be understood as a compensatory, albeit dysfunctional response to sympathetic overactivity. Interestingly, vagal nerve stimulation has been documented to reduce histamine-induced itch in humans (14), although the exact central (or spinal) mechanisms for this effect have not yet been elucidated.

As seen in previous studies, the AD group had a lower moisture retention and a higher TEWL compared with healthy controls (41). Psychological stress has been shown to impair skin barrier function in healthy subjects (42). We hypothesized that skin barrier impairment would be accentuated in response to acute stress in AD, but this study was unable to demonstrate it. The results of palm corneometry and palm TEWL were unexpected, showing diminished response to acute itch, scratching and mental stress in both the healthy and AD group. Future studies are necessary to clarify the effect of histamine-induced itch on different measures of sweating.

Chronic itch shares similar neural pathways with chronic pain (43). Chronic itch and chronic pain both involve peripheral and central sensitization of nerve fibers (44, 45) and therefore these conditions may respond similarly to acute stress. Previous studies of chronic pain of fibromyalgia and irritable bowel syndrome showed an altered sympathetic and parasympathetic tone in response to an acute painful stressor (46, 47). The results of this study show a similar HRV response in AD where itch and scratching act as acute stressors.

Psychological stress has been thoroughly studied and undoubtedly plays a role in the chronically relapsing course of AD and chronic itch (48). However, there is scant information about the exact role of the ANS when patients are exposed to itch and scratch in the background of a pre-existing atopic condition. An altered neuroendocrine regulation of the hypothalamic-pituitary-adrenal (HPA) axis is known to contribute to active disease in AD, and recent studies have begun to elucidate the role of the ANS in the mechanism of itch (16, 49). Therefore, measuring autonomic function following acute stress rather than at rest provides critical information for a stress-responsive condition such as atopic eczema.

Chronic itch, which may be somatic, emotional and cognitive, may be treated with therapies that can modulate the ANS stress response. Behavioral biofeedback techniques and psychotropic drugs that reduce stress and anxiety have been used to treat chronic pain and could potentially alter the sympathetic over-activity noted in patients with AD (50–53). Patients with AD with an extreme sympathetic response (such as those seen in this study with significantly elevated VLF), may particularly be candidates for such therapy. A recent study showed that integrative body-mind training results in a better regulation of the ANS through the anterior cingulate cortex (40), and these findings could potentially be developed for specific interventions in chronic itch conditions such as AD.

Although patients with a history of psychiatric disease or taking anxiolytic medication were excluded, a limitation of this study was that we did not examine the degree of anxiety and depression of the participants. Anxiety and depression can influence HRV independently (49). Additionally, the majority of patients with AD in this study had moderate atopic disease. Further studies addressing both disease severity and HRV under acute stress will help to clarify the role of the ANS in AD.

In conclusion, this study reveals evidence of ANS dysfunction in patients with AD. The possibility of an impaired parasympathetic response in chronic itch has received little attention; further studies exploring ANS dysfunction in AD are therefore warranted.

The authors declare no conflict of interest.

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