Acta Derm Venereol (Stockh) 1991; 71: 219–223

Local Cholinergic Sweat Stimulation in Atopic Dermatitis

An Evaporimetric Study

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In atopic dermatitis the nature of potential sweating disturbances is still obscure. Using an evaporimeter, local sweating response to a supra-threshold concentration of methacholine and baseline water loss were measured from non-eczematous back skin of 167 young males in five main groups (pure atopic dermatitis, atopic dermatitis with rhinitis/asthma, rhinitis/asthma, non-atopic dermatosis, and non-atopic healthy). Subjects with atopic dermatitis were further divided into two subgroups: dry-looking and normal-looking back skin. Compared with non-atopic healthy individuals, the sweat loss was significantly depressed ($p < 0.01$) and the baseline water loss significantly increased ($p < 0.001$) in the main groups with atopic dermatitis. Both these trends were most distinct in atopic dry-looking skin, whereas in normal-looking atopic skin only the sweat loss was depressed ($p < 0.05$). Respiratory atopy had no effect on the sweating response. No significant correlation was found between the individual baseline water loss and the sweating response. ***Key words: Sweating, Water loss.***

(Accepted October 29, 1990.)

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Sweat gland function in atopic dermatitis (AD) has been a subject of contradictory reports. Earlier studies by Sulzberger and his co-workers suggested that there was an impairment of sweat delivery caused by horny plugging of the sweat duct ostia (1) or by periostial edema (2). However, there was no histological evidence of plugging (3). In later studies, hypohidrosis has not been regarded as an important aspect in AD. Instead, increased local sweating following cholinergic stimulation was reported both in patients with AD (4, 5) and in patients with respiratory atopy (6). This hyperreactivity was proposed to result from beta-adrenergic hyporeactivity (7).

In a previous study we were unable to confirm sweat gland hyperreactivity when using methacholine as the cholinergic local stimulant in non-eczematous back and forearm skin in patients with AD (8). Since hyperreactivity even to low concentrations of cholinergic stimulants has been reported in atopic patients (5, 6), a near-threshold concentration of methacholine was chosen as the test substance for the present study. Evaporimetry was used to measure both the sweating response and the baseline water loss in atopic and non-atopic young males.

MATERIAL AND METHODS

Subjects

Informed consent was obtained from all 167 male participants (conscripts: mean age 20.6 years, range 17–27). The atopics were divided into three main groups and the non-atopics into two main groups: atopic dermatitis (AD pure, $n = 30$), AD with rhinitis/asthma ($n = 48$), rhinitis/asthma alone ($n = 23$), non-atopic dermatosis ($n = 42$) and non-atopic healthy ($n = 24$). The AD subjects were further divided according to the clinical condition of their back skin into subgroups: AD normal skin ($n = 38$) and AD dry skin ($n = 40$).

The skin lesions in the AD subjects accepted for study were mild to moderate (9, 10) and the non-eczematous back skin appeared either smooth and shiny (AD normal), or dry, rough, and slightly to moderately scaling (AD dry). The subjects with rhinitis and/or asthma were free from dermatosis. Subjects with non-atopic dermatosis had other mild skin affections. Exclusion criteria were: subjects with severe atopic dermatitis with or without ichthyosis, emotional hyperhidrosis or overt eczema involving the back skin.

Topical and/or peroral medication was discontinued at least 5 days and phototherapy or suntanning at least one month prior to testing.

Environmental conditions

Tests were performed during two consecutive winter periods from October to April in a normal laboratory room. The ambient room temperature ranged from 21° to 23°C and the relative humidity was between 25% and 35%.

Test procedure

The subjects rested supine with the upper part of their body uncovered for an adaptation period of 15 to 20 min. Local skin temperatures were measured at the least involved symmetrical test sites 7 to 9 cm paraspinally on the upper

Table I. *Total cutaneous water loss (CWL), baseline water loss (BWL) and 'pure' sweat loss (SL) rates (g/m^2h) in the main groups and subgroups of atopic dermatitis*

Group	CWL mean (SD) median	BWL mean (SD) median	SL mean (SD) median
AD pure	62.1 (32.4) 54.4**	12.0 (5.5) 10.8***	50.1 (33.7) 45.7**
AD rhinitis, asthma	62.4 (37.8) 59.7*	11.2 (4.4) 10.2***	51.2 (37.4) 52.4**
Rhinitis, asthma	71.6 (39.0) 67.2	7.1 (2.0) 6.5	64.5 (38.5) 60.0
Non-atopic dermatosis	74.0 (27.8) 79.2	8.5 (3.3) 7.6	65.5 (27.7) 71.1
AD with dry skin	61.1 (38.8) 48.7*	14.7 (4.5) 13.8***	46.4 (38.8) 31.4**
AD with normal skin	63.4 (32.4) 62.1*	8.1 (2.0) 8.2	55.3 (32.2) 55.0*
Non-atopic healthy	79.7 (30.4) 74.6	7.5 (2.0) 6.8	72.2 (30.6) 68.8
	ap>0.05	*ap*<0.001	*ap*<0.05

Significance level vs. non-atopic healthy: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ (Wilcoxon rank sum test adjusted by Bonferroni method).
a Significance level of ANOVA test.

back skin (Exacon Scientific Instruments, Taastrup, Denmark). The baseline water loss (BWL), and after sweat stimulation the peak cutaneous water loss rate (CWL), which was reached within 2–3 min, were recorded. BWL was preferred instead of the term transepidermal water loss (TEWL) because the sweat gland function was not inhibited by an anticholinergic drug. Evaporative rates were measured with an evaporimeter (Evaporimeter EP 1, ServoMed, Sweden) (11). The 'pure' sweat loss (SL) was calculated by subtracting BWL from the corresponding CWL. The individual data were averaged and expressed as g/m^2h.

Methacholine chloride (Mecholyl, Sigma) diluted in saline, was used at a near-threshold concentration 5×10^{-7} mol/l. A volume of 0.1 ml was injected intradermally with a 27-gauge needle introduced from outside the periphery of the test site (12).

Statistical analysis

One-way-analysis of variance (ANOVA I) was used for testing the groups and the subgroups. Wilcoxon rank sum test adjusted by the Bonferroni method was employed to compare the main groups and the AD subgroups with the non-atopic healthy group. Student's *t*-test was used to compare the BWL/CWL ratios. The association of BWL and SL values was calculated by using the Spearman rank correlation test.

RESULTS

The results from all groups are presented in Table I. The mean and median sweat responses (CWL, pure SL) were highest in the two non-atopic groups. Compared with non-atopic healthy controls, the median SL levels were significantly lower in all four AD groups. The sweating response was the lowest in AD with dry skin, the median SL level being 54% lower than found in healthy controls. In contrast, AD with normal skin gave a value only 22% lower than in non-atopic healthy. The CWL and SL rates demonstrated equal trends, except that the group differences in SL rates were more distinct. SL levels in AD groups with and without respiratory symptoms did not differ markedly from each other, nor did the levels in rhinitis/asthma from those of the two non-atopic groups.

The BWL levels in AD main groups were high and did not differ from each other. The mean value was highest in AD with dry skin. Instead, in AD with normal skin and in rhinitis/asthma alone the mean

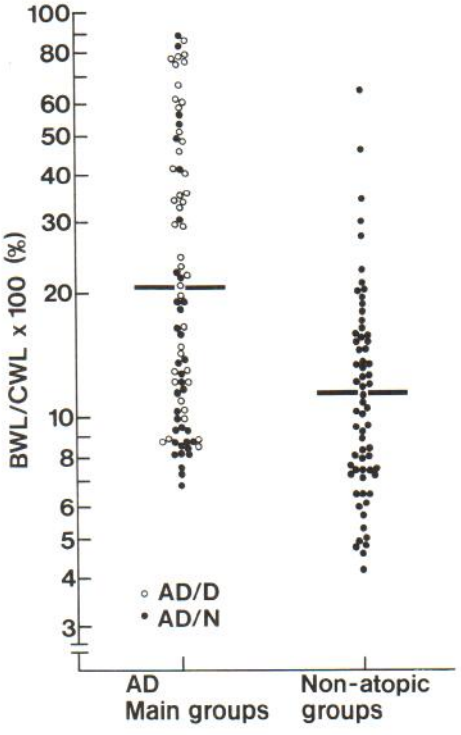

Fig. 1. BWL/CWL ratios of AD and non-atopic subjects; BWL expressed as per cent of the corresponding CWL rate. AD/D = AD with dry skin, AD/N = AD with normal skin.

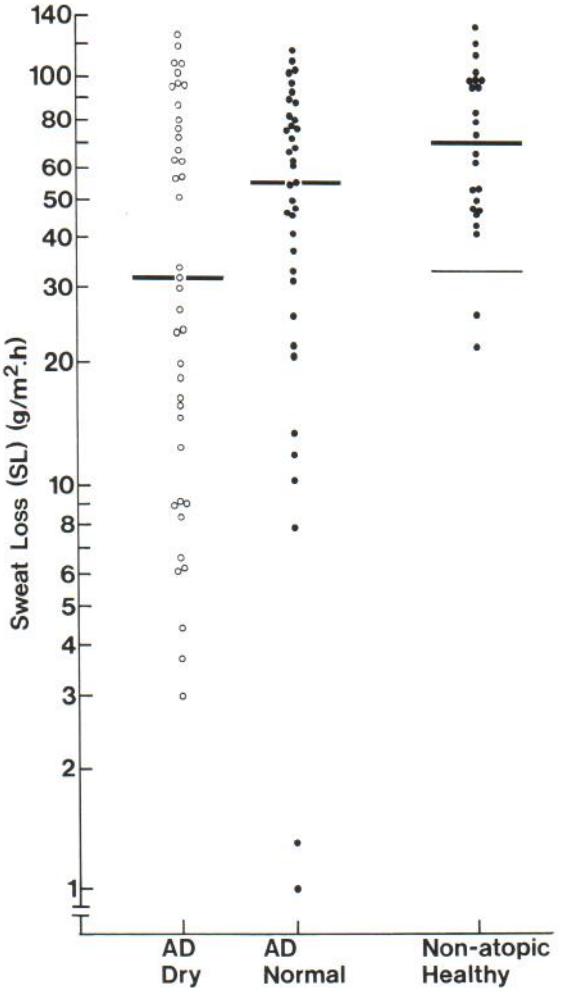

Fig. 2 a. Individual and median sweat loss (*SL*) rates in AD with dry skin, in AD with normal skin and in non-atopic healthy. The thin line indicates the lower decile for non-atopic healthy (32.8 g/m²h) defined as the lower limit for normal SL.

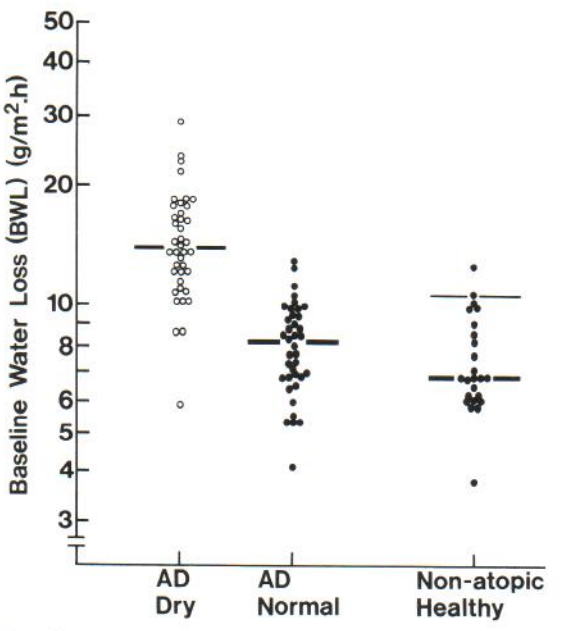

Fig. 2 b. Individual and median baseline water loss (BWL) rates in AD with dry skin, AD with normal skin and in non-atopic healthy. The thin line indicates the upper decile for non-atopic healthy (10.5 g/m²h) defined as the upper limit for normal BWL.

BWL levels did not differ essentially from those found in the non-atopic groups.

The group variations in the water loss data were not explained by differences in local skin temperature, since the mean difference in AD main groups vs. non-atopics was 0.07°C ($p > 0.05$).

In order to evaluate the combined effects of the baseline water loss and the sweating response on inter-group differences, the individual BWL to CWL ratios were calculated. In AD vs. non-atopics, the logarithmic means, expressed in percentage values, were 20.8% and 11.2% ($p < 0.001$) (Fig. 1). In AD with dry skin vs. non-atopic healthy, the corresponding figures (28.4% and 9.8%) showed a three-fold difference whereas separately, the BWL rates showed a two-fold difference and the SL rates approximately a 1.5-fold difference (Table I).

Although both the low SL and the high BWL rates were concentrated on the AD groups, only poor or non-existent inverse correlations were observed between individual SL and BWL rates in the whole series ($r = -0.11$), in AD with dry skin ($r = -0.19$)

Table II. *Subjects with depressed SL, and depressed SL plus elevated BWL*

Group	Depressed SL (%)	Depressed SL plus elevated BWL (%)
AD main groups	41	27
AD with dry skin	50	43
AD with normal skin	29	8
Rhinitis/asthma	28	0
Non-atopic groups	11	0

Depressed SL, any value below the lower decile (32.8 g/m²h) in non-atopic healthy; elevated BWL, any value above the upper decile (10.5 g/m²h) in non-atopic healthy.

and in the other groups. For a frequency analysis of abnormal individual values the lower decile of the SL data and the upper decile of the BWL data in the group of non-atopic healthy controls were arbitrarily defined as normal limits. In other groups, data outside these limits were regarded abnormal, i.e. either 'depressed' SL or 'elevated' BWL. Any values outside the reciprocal deciles in the control group were considered normal (Fig. 2a, b). 'Elevated' BWL occurred in 53% of AD pure, in 46% of AD with rhinitis/asthma, in 85% of AD with dry skin, in 11% of AD with normal skin and in 9–16% of other groups. As shown in Table II, 'depressed' SL rates or coexistence of both abnormalities occurred most frequently in AD with dry skin, in a few AD subjects with normal skin, but in none of the subjects with rhinitis/asthma or the non-atopics.

DISCUSSION

Our high BWL data in AD agree with previous findings on TEWL from other skin areas (13, 14, 15) and with Werner & Lindberg (16), who also found higher TEWL rates in dry than in normal AD back skin. Our data also showed that respiratory symptoms alone or associated with AD did not have any noticeable effect on BWL rates.

The present sweat response studies were carried out using a concentration tenfold higher than the threshold methacholine concentration (12). When measuring low sweat outputs, it is important to distinguish pure sweat loss (SL) from total stimulated cutaneous water loss (CWL), since the proportion of BWL in CWL rates was up to three times higher in AD groups than in the other groups. Otherwise the lowered SL rates in AD would have been partly obscured under CWL data, which therefore did exhibit smaller group variations than the SL data (Table I).

The present SL responses in AD groups with or without respiratory symptoms were one-third lower than in the non-atopic healthy, whereas the rhinitis/asthma group responded normally. In contrast, Warndorff (5) found elevated sweating responses in AD and asthma to a supra-threshold concentration of acetylcholine, and Kaliner (6) reported elevated sweat responses to methacholine in respiratory atopics. Both authors used the forearm as their test site. However, in a previous study we were unable to demonstrate any elevated sweat responses to methacholine in normal forearm skin in AD (8). Also, later results on AD forearm skin demonstrated normal counts of sweat glands activated by acetylcholine (17). Thus the claims for cholinergic sweat gland hyperreactivity in atopy (5, 6, 7) are not supported by these results.

Because in AD groups – and particularly in AD with dry skin – depressed SL and elevated BWL were most frequent (Table I), an association between these distinct water loss functions seems likely. However, no significant inverse correlation was found between the individual BWL and SL rates in any group. This lack of correlation could derive from non-ideal ambient conditions, emotional upset or too short an adaptation period (18, 19), all leading to false water loss rates. However, a reasonably good reproducibility was obtained with this same technique under identical conditions (12). More probably the potential correlation between BWL and SL was obscured by the very wide interindividual variations in the sweating response. In addition, there is no reason to believe that, in normal skin, sweating capacity is related to its BWL rate. However, high BWL rates and low SL rates may be somehow indirectly related, e.g. both abnormalities may result from a skin irritant stimulus, but they may occur and disappear with a different time course.

The cause of the hypohidrotic response mostly observed in dry AD back skin is not yet clear. The water content of the horny layer in dry atopic skin and its water-binding capacity seem to be reduced (20, 21, 22). These changes, obviously related to deficient epidermal, sebaceous and horny layer lipids (23, 24), may explain the abnormal barrier function.

Dry atopic skin surface shows an irregular pattern (25). In our AD patients, occlusive and rough military clothing may have led to subclinical irritation, elevated BWL and to overhydration of the inherently abnormal horny layer. These factors may further contribute to increased epidermal thickness and to increased cohesion between corneocytes (15), and eventually to closure of sweat duct ostia somehow reminiscent of miliaria.

In this study we found a lowered sweating response in AD with a weak methacholine stimulus. However, we have also observed a reduced sweating response in AD when using a near-maximal methacholine stimulus and a gravimetric sweat collection method (manuscript submitted).

In conclusion, the sweating response to methacho-

line stimulation was hypohidrotic in AD, particularly in dry-looking skin, which also showed the highest baseline water loss rates. On the other hand, respiratory atopy increased neither the sweating nor the baseline water loss rates.

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