

Effects of Occlusion on the Skin of Atopic Dermatitis Patients

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Background: Atopic dermatitis (AD) may be exacerbated by occlusion from items such as occlusive gloves or textiles, especially if the occlusion is removed suddenly, creating a steep humidity gradient. Most previous studies of occlusion have focused on normal skin. Occlusion has been shown to be beneficial in psoriatic skin, but many atopic patients complain of increased inflammation after occlusion.

Objective: To evaluate the response of noninflamed AD skin to occlusion.

Methods: Six patients with AD were patch-tested with occlusive polyethylene wrap and sodium lauryl sulfate (SLS) in standard Finn Chambers taped to noninflamed skin of the back. Cytokine and chemokine messenger ribonucleic acid (mRNA) for interleukin-8 (IL-8), interleukin-1 alpha (IL-1 α), and interleukin-1 receptor antagonist (IL-1RA), as well as the 18S rRNA housekeeping gene, was obtained via tape-stripping the skin and measured using quantitative real-time polymerase chain reaction. We also measured transepidermal water loss after removal of occlusion.

Results: Polyethylene occlusion alone with abrupt removal induced IL-8 and IL-1 α levels similar to or exceeding that of SLS. IL-1RA was up-regulated by SLS and occlusion, with SLS showing a stronger response.

Conclusion: Removal of occlusion with polyethylene film up-regulates the inflammatory cytokines IL-8, IL-1 α , and IL-1RA in patients with AD. This may explain the worsening of AD with the use of occlusive gloves, athletic equipment, and fabrics.

OCCCLUSION can be beneficial in inflammatory skin disease such as psoriasis but may be detrimental in atopic dermatitis. Filaggrin deficits in atopic dermatitis make skin more likely to fissure when a steep humidity gradient is present after the rapid removal of occlusion; defects in innate immunity make bacterial colonization more likely in atopic skin, and occlusion worsens bacterial proliferation as well.

Patients with atopic dermatitis differ from normal or psoriatic patients in their clinical tolerance of occlusion. In our experience, atopic patients complain more of itching from tape occlusion associated with patch testing and experience flares of dermatitis in areas of occlusion, such as the area under soccer shin guards or covered by occlusive footwear or fabrics. Occupation-related hand dermatitis due to "wet work" has long been recognized as more common among atopic patients; surfactants are often blamed, but a study on pig skin implicated water itself as the most likely culprit.¹

We studied the effect of polyethylene occlusion on normal skin of patients with atopic dermatitis. Occlusive gloves, dressings, and fabrics are all relevant clinical examples of occlusion in the cutaneous environment.

Patients and Methods

Messenger ribonucleic acid (mRNA) produced by the skin was measured with quantitative real-time polymerase chain reaction (PCR) after a short period (6 hours) and a prolonged period (4 days) of patients' wearing the occlusive wrap and sodium lauryl sulfate (SLS). No inflammatory cytokines were found at 6 to 8 hours, so the 6-hour measurement was omitted for the last three subjects, in which inflammatory responses were measured only at the prolonged period (4 days). Changes of mRNA in interleukin-1 alpha (IL-1 α), interleukin-1 receptor antagonist (IL-1RA), interleukin-8 (IL-8), and the housekeeping gene eukaryotic 18S rRNA were measured. mRNA markers were cytokines found to play a role in inflammatory response in the skin either through exacerbating (IL-1 α , IL-8) or inhibiting (IL-1RA) inflammation.² These inflammatory markers have been shown to be induced by SLS, our positive control.³ 18S rRNA was used as a housekeeping gene because the expression of ribosomal RNA has been shown to be

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more stable than other commonly used housekeeping genes.^{4–8}

Although biopsy is commonly used for the clinical investigation of the skin, this invasive method could have caused discomfort for patients participating in the study. To minimize patients' discomfort, we opted to obtain RNA for our study by using tape stripping, a technique previously shown to successfully isolate RNA from skin samples.^{9–12} Benson and colleagues showed that large quantities of total RNA could be recovered from psoriatic skin via tape stripping and that tape stripping was sensitive enough to reveal mRNA markers that were undetected in biopsy specimens.¹²

Clinical Protocol

Six subjects with a history of atopic dermatitis (AD) were included. To establish the diagnosis, subjects were required to meet two of three modified Hanifin and Rajka criteria¹³: (1) chronic or relapsing eczema, (2) chronic itching affecting flexural surfaces in adults and affecting the face and extensors in infants, and (3) a personal or family history of hay fever or asthma. Exclusion criteria included the use of any topical medications on the areas of skin to be studied for 2 weeks prior to the study, current use of systemic immunosuppressants, significant exposure to natural sunlight (such as outdoor tanning) or tanning salons for 1 week prior to the study, and pregnancy. The study was approved by the University Hospitals of Cleveland Case Medical Center Institutional Review Board (#10-07-11), and informed consent was obtained from all participants.

Subjects removed heavy garments and equilibrated at room temperature for 30 minutes before the start of the study. For all subjects, the room humidity was 22.1 to 22.3%, and the room temperature was 26° to 27.7°C.

The skin of the back adjacent to the posterior axillary lines was cleaned with an alcohol pad, and a 4 × 4 cm piece of occlusive polyethylene wrap (SC Johnson Company, Racine, WI) was applied to symmetrically located sites bilaterally. Inferior to the occlusive site, a cluster of three 11 mm patch-test chambers with filters (Epitest Ltd Oy, Tuusula, Finland) each containing 30 µL of 1% SLS (Sigma-Aldrich, St. Louis, MO) was applied bilaterally. A waterproof dressing (Medline Industries Inc., Mundelein, IL) was applied over the occlusive and SLS sites to help secure the materials.

The second patient visit (subjects 1, 2, and 3 only) was 6 to 8 hours after patch application. The occlusive wrap

and SLS sites were tape-stripped with D-squame adhesive 22 mm sampling discs (CuDerm Corporation, Dallas, TX), which were applied, rubbed vigorously for 10 seconds, and then removed. Twenty adhesive discs were used per site. SLS sites were tape-stripped 30 minutes after patch removal because SLS sites gradually develop more inflammation after patch tests are removed.¹⁴ Additional occlusive dressings and SLS patch-test chambers were applied adjacent to the tape-stripped sites, to be measured at 4 days.

The third patient visit took place after 4 days, and tape stripping was done in the same way it was done at the second visit. All six subjects participated in the study during the winter months of December through February. None of the subjects had active dermatitis on the skin of the back. Consistent areas of skin were sampled for each material and each subject.

RNA Isolation

Twenty tape strips were obtained for each subject at every sampling site. The first 10 tapes from each site were discarded because we demonstrated via real-time PCR that mRNA was more abundant in the last 10 tapes (data not shown). The remaining 10 tapes were collected individually in 2 mL cryogenic vials, with the adhesive side facing inward, and stored at –80°C until processed. We added 1.5 mL of Buffer RLT (Qiagen, Valencia, CA) to the first cryogenic vial from each site. The vial was then inserted into a Braun Mikro Dismembrator (B. Braun Biotech Inc., Allentown, PA) and shaken vigorously for 2 minutes at 2,000 rpm. The vial was spun in a centrifuge at 3,000 rpm for 3 minutes at 20°C. The RLT buffer was then transferred to the next cryogenic vial in the tape series, and the process was repeated until all 10 tapes from a site were processed in the same RLT buffer. After all tapes were processed, RNA isolation was accomplished with an RNeasy Kit (Qiagen) according to the manufacturer's instructions.

Reverse Transcription and Quantitative Real-Time PCR

RNA samples were reverse-transcribed into complementary deoxyribonucleic acid (cDNA) with random hexamers using the SuperScript III First-Strand Synthesis System (Invitrogen, Carlsbad, CA) for real-time PCR (RT-PCR). Eight microliters of RNA template were used in each cDNA reaction, in a final volume of 21 µL. RT-PCR using a TaqMan Universal PCR Master Mix (Applied Biosystems, Foster City, CA) was performed with 1.5 µL of cDNA per

reaction. All reactions were run in triplicate with nontemplate controls. The specific inventoried TaqMan gene expression assays (Applied Biosystems) used included eukaryotic 18S rRNA (Hs99999901_s1), IL-8 (Hs00174103_m1), IL-1 α (Hs00174092_m1), and IL-1RA (Hs00277299_m1). The mRNA levels of the targets were measured on the ABI Prism 7700 Sequence Detection System (Applied Biosystems). PCR was performed under the following conditions: 2 minutes at 50°C and 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C and 1 minute at 60°C. Dilution experiments were performed to ensure similar efficiency of the PCR primer/probe sets.

PCR data are reported as the cycle threshold (Ct) necessary to achieve fluorescence. Ct values of 37 or greater were considered to have mRNA that was undetectable because Ct values beyond 37 become highly variable or fluorescence does not achieve a threshold value.¹⁰ The relative expression levels of each gene were calculated according to the comparative, or $\Delta\Delta\text{Ct}$, method.^{15–17} The Ct values of triplicate RT-PCR reactions were averaged for each gene in each cDNA sample. For each sample assayed, the average fluorescent reporter dye FAM (6-carboxy-fluorescein) Ct value for the gene of interest was subtracted from the average FAM Ct value of 18S rRNA to obtain the ΔCt value. The $\Delta\Delta\text{Ct}$ value was calculated by subtracting the average ΔCt (calibrator) values from the ΔCt (sample). The relative quantification was calculated by $2^{-\Delta\Delta\text{Ct}}$. The mRNA quantity for the calibrator is expressed as $1 \times$ sample, and all other quantities are expressed as a fold difference relative to the calibrator. The mean ΔCt of the SLS was used as the calibrator in all tests. The standard deviation values for $\Delta\Delta\text{Ct}$ were added to or subtracted from the $\Delta\Delta\text{Ct}$ to generate the upper and lower $\Delta\Delta\text{Ct}$ standard deviation boundaries. These $\Delta\Delta\text{Ct}$ values were then transformed ($2^{-\Delta\Delta\text{Ct} \pm s}$, where “s” equals the standard deviation of the $\Delta\Delta\text{Ct}$ value) to generate error bars. In all statistical analyses, significance was assessed by means of Student’s *t*-test, and $p < 0.05$ was considered significant.

Results

Transepidermal Water Loss

Table 1 shows the mean change in transepidermal water loss (TEWL) for the five subjects measured. TEWL was significantly increased by occlusion alone and to a greater extent by SLS under occlusion.

Table 1. Mean Change in Transepidermal Water Loss (Baseline to Day 4 for All Subjects)

Material	Δ TEWL	Standard Deviation	p Value
Occlusion ($n = 5$)	14.1	7.5	.014
SLS ($n = 5$)	35.7	19.4	.015

SLS = sodium lauryl sulfate; TEWL = transepidermal water loss.

mRNA Expression

Cytokine mRNA data from tape stripping for individual subjects are shown in Table 2. At day 4, IL-8, IL-1 α , and IL-1RA mRNA was induced by occlusion alone and SLS in all patients (with the exception of patient 6, who did not express IL-8 or IL-1 α in response to occlusion). Expression of IL-8 mRNA under polyethylene occlusion alone was 2.17-fold greater than with SLS ($p < .001$) whereas expression of IL-1 α under polyethylene occlusion was not



Figure 1. Day-4 patch-test sites: *top*, site of sodium lauryl sulfate in three adjacent Finn Chambers; *bottom*, site of a square piece of polyethylene wrap. Both patch tests were removed at day 2.

Table 2. Average-Fold Change in Target:18s mRNA Ratio in Occlusion Alone, Relative to Sodium Lauryl Sulfate

Target	n	Average-Fold Change Relative to		
		SLS	95% CI	p Value
IL-8	5	2.17	1.93–2.43	< .001
IL-1 α	5	1.10	0.92–1.32	> .50
IL-1RA	6	0.56	0.48–0.64	.001

CI = confidence interval; IL = interleukin; IL-1RA = interleukin-1 receptor antagonist; SLS = sodium lauryl sulfate.

significantly different when compared to SLS (see Table 1). Expression of IL-1RA was significantly lower under polyethylene occlusion than with SLS (a 0.56-fold change [$p = .001$]) (see Table 2).

Figure 1 shows the objective inflammation visible under occlusion and under the SLS patch site on the subject who had the most visible inflammation at the site of polyethylene occlusion alone. (Some subjects had no visible inflammation at this site.)

Discussion

We showed that polyethylene occlusion of AD skin induced an inflammatory immune response that was visible in some cases and detectable with RNA isolated from tape-stripped areas of skin. We were able to replicate previous studies that used tape stripping to measure mRNA produced by the skin.^{9–12} However, these studies did not include patients with AD. We showed that occlusion with polyethylene wrap induced mRNA for IL-8, IL-1 α , and IL-1RA in our subjects. Occlusion induced significantly more mRNA for IL-8 (a proinflammatory chemokine) than did SLS and induced significantly less IL-1RA mRNA (an antiinflammatory cytokine) than did SLS. Similar amounts of IL-1 α mRNA were induced by occlusion and SLS. Our results thus show that with AD patients, occlusion with polyethylene can cause irritation to the skin similar to that caused by SLS, a known irritant.

Keratinocytes manufacture cytokines; the most common constitutively expressed cytokine is the proinflammatory cytokine IL-1 α . In normal mouse skin, latex occlusion for 24 to 48 hours significantly reduces IL-1 α .¹⁸ However, after acute barrier disruption with acetone or tape stripping, occlusion does not lessen either IL-1 α or other inflammatory cytokines.¹⁸

Clinically, occlusion is known to be poorly tolerated by AD patients; however, supporting literature investigating the mechanism of action for this observation is sparse. Evidence in normal subjects suggests that occlusion may

obstruct skin ventilation and compromise skin barrier function, which may exacerbate dermatitis.^{19,20} In a study comparing the unaffected skin of atopic, psoriatic, and normal individuals in response to plastic occlusion of the forearm for 2 days, the water-retention capacity of AD patients was shown to be significantly less than that of normal or psoriatic patients, whereas TEWL was significantly increased.²¹

In psoriasis cases, occlusion is a well-established treatment that has been shown to improve outcomes.^{22–24} In hairless mice, occlusion appears to prevent increases in DNA synthesis that may contribute to epidermal hyperplasia.²⁵ Rapid drying after occlusion is removed may explain the observation that low humidity contributes to the seasonal exacerbation of some inflammatory dermatoses. In a study of 10 nonatopic patients, TEWL was increased 10 minutes after the removal of occlusive polyethylene wrap worn for 3 days.²⁶

Leow and Maibach cite examples of improved wound healing in normal skin with occlusion but also review data showing that water-impermeable materials delay the repair of barrier damage in mice.²⁷ AD is linked to a defect in the filaggrin gene, which causes impaired barrier function.²⁸

Filaggrin defects have been found in both European and Japanese AD patients.²⁹ The decreased integrity of the epidermis due to defects in adhesion molecules may make AD skin more likely to fissure during rapid drying. Frequent wet-to-dry cycles (from high-humidity occluded skin rapidly drying when occlusive gloves are removed in low-humidity air) are a common cause of wintertime occupational hand dermatitis in patients who do “wet work.” TEWL increases transiently after occlusive gloves are worn for 4 hours and TEWL is measured 20 minutes after the gloves are removed.³⁰ Upon the removal of occlusion, atopic skin may be more likely to fissure and become inflamed due to filaggrin defects. Juvenile plantar dermatosis is another clinical model for the detrimental effects of occlusion combined with moisture from perspiration in atopic children.

Adhesion defects such as those due to filaggrin may also allow protein antigens to penetrate past the stratum corneum; AD patients are particularly likely to have an allergic response to protein allergens. Occlusion causes the proliferation of commensal yeast such as *Malassezia sympodialis*.²⁶ In AD patients, the yeast causes delayed-type hypersensitivity that manifests as dermatitis of the skin on the head, neck, and upper torso where sebaceous activity is sufficient to support yeast growth. Adult patients with dermatitis of the neck and upper torso in areas of maximal contact with clothing often react to patch tests with this yeast.³¹

Another possible explanation for our findings may be related to microbial overgrowth under the occlusive material. IL-1 α levels have been shown to increase in the skin of mice during *Staphylococcus aureus* infection.³² Patients with AD are known to be markedly susceptible to cutaneous infection with bacteria, fungi, and viruses,³² and cutaneous superinfection with *S. aureus* is elevated even in healthy-appearing skin of AD patients when compared to unaffected controls.³³ Microbes can invade the skin after skin barrier disruption, and the innate immune system responds to these pathogens. One mechanism of innate immunity includes antimicrobial peptides (such as human β -defensin 2 and LL-37, a cathelicidin), which are induced by injury or inflammation of the skin.^{33,34} Patients with AD have been shown to be deficient in these peptides, which are effective against bacteria, viruses, and fungi. Specifically, the quantities of these peptides found in AD patients were insufficient to be effective in killing *S. aureus*.³⁵

Shin guard dermatitis is observed in athletes who wear shin guards, and patch-testing with all components of the shin guards often yields negative results.³⁶ This condition is more common among patients with AD.³⁷ Occlusion plays a role in this condition, which may be partly due to irritation from sweating under the shin guard, microbial proliferation, and barrier damage from drying after shin guard removal.

Limitations

The limitations of the current study include the small number of subjects; thus, the analyses cannot be regarded as definitive. Additionally, no nonatopic controls were analyzed; further investigation is therefore needed to discern whether the induction of inflammatory cytokines by occlusion is truly limited to atopic patients. The cytokine profile we selected to evaluate was limited to very specific markers known to be associated with inflammation. Additional cytokine and chemokine mRNA profiles would be desirable and necessary to demonstrate more definitively the extent of mRNA changes associated with occlusion of the skin of AD patients. Further, differences in the time course of mRNA expression may have existed between occlusion and SLS, and it is possible we did not do our tape stripping at the time of peak mRNA expression. It also would be worthwhile in future studies to do cultures to see if additional microbes are present in occluded versus non-occluded skin. Nonphysiologic bacterial flora are increased under synthetic fibers when compared to less occlusive cellulose fibers.³⁸

Finally, it is not known whether these findings extend to other types of occlusion.

Treatment Implications

Our results show that occlusion with polyethylene disrupts AD skin, a finding that we have observed clinically as well. Although the specific mechanism whereby occlusion worsens barrier function in AD remains to be elucidated, this finding has many clinical implications. Filament polyester and nylon fabrics are occlusive. Polyester has been shown to be irritating to the skin. Yao and colleagues compared subjects wearing cotton or polyester pajamas for 3 weeks and found that mean stratum corneum water content was significantly higher in those wearing cotton pajamas. There was a significant improvement in stratum corneum water content when subjects changed from polyester to cotton, coupled with a significant decline when subjects changed from cotton to polyester.³⁹ Nylon clothing was also recently found to cause flares of eczema in children.⁴⁰ Nonfilamentous cellulosic fibers such as cotton or lyocell are preferable for AD patients.

Occlusion remains a popular treatment for inflammatory skin diseases in general, most likely due to the evidence supporting its efficacy in treating psoriasis. Our data suggest that occlusive treatments such as sauna suits or plastic dressings should be reconsidered and further studied in AD patients. The penetration of antiinflammatory topical medications is enhanced by occlusion such as plastic tape and may outweigh the inflammatory effects of occlusion itself in some circumstances (such as on lichenified skin). However, transdermal medication delivery may cause irritation in AD patients.⁴¹ Occlusive ointment therapy was not addressed in our studies; we speculate that gradual change in the humidity gradient as ointments are gradually removed from the skin surface may be less damaging than the abrupt removal of occlusive dressings, clothing, or athletic gear. We also did not study more-complex occlusive systems such as diapers, which include absorptive layers and retain urine, which may alter the regional microbiome.

Additional investigation of the mechanism of occlusion and its effects on AD is warranted to improve quality of life for AD patients and to refine recommendations for protective equipment, apparel, and topical vehicles for these patients.

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