

ORIGINAL ARTICLE

Evaluation of positive patch test reactions using optical coherence tomography: A pilot study

Ali Rajabi-Estarabadi  | Darren C. Tsang  | Keyvan Nouri | Antonella Tosti

Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA

Correspondence

Ali Rajabi-Estarabadi, MD. Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA.
Email: arajabi@med.miami.edu

Abstract

Introduction: Patch testing is the gold standard for evaluating allergic contact dermatitis (ACD), yet current interpretation methods are limited by their subjectivity and possible variability between observers. Optical coherence tomography (OCT) imaging enables noninvasive in vivo skin visualization and holds promise as an objective method of patch test interpretation.

Objective: To evaluate the micromorphological changes of patch test reactions and identify objective, quantitative OCT markers that correlate with clinically graded patch test reactions.

Results: A total of 25 patch test reactions (7 grade-0, 4 grade-1+, 14 grade-2+) from 7 patients underwent OCT evaluation. Increased epidermal thickness and density was qualitatively observed in grade 1+ and grade 2+ allergic reactions while well-demarcated, signal-free cavities were observed in all grade 2+ reactions. Attenuation coefficients significantly increased across the three reaction grades (2.58 ± 0.092 , 2.96 ± 0.121 , 3.05 ± 0.065 ; $P < 0.01$). Cutaneous blood flow at 0.35 mm monotonically increased with reaction grade severity and blood measurements significantly differed across the three reaction grades (0.053 ± 0.011 mm/s, 0.078 ± 0.015 mm/s, and 0.121 ± 0.008 mm/s; $P < 0.01$).

Conclusions and Relevance: Attenuation coefficient and cutaneous blood flow at 0.35 mm correlate with clinically graded patch test reactions and hold promise as objective, quantitative markers. OCT may help dermatologists differentiate clinical scoring of allergic reactions in patch test and thereby improve their diagnostic accuracy and interpretation of patch test reactions.

KEYWORDS

allergic contact dermatitis, evaluation, optical coherence tomography, patch test

1 | INTRODUCTION

Contact dermatitis is a common skin problem which accounts for nearly 5.7 million physician visits annually.^{1,2} Patch testing is the gold standard for evaluating patients with suspected allergic contact dermatitis (ACD).³ Dermatologists routinely evaluate patch tests by means of visual inspection and palpatory findings. Precise

reading and interpretation of patch test reactions are challenging and require an experienced clinician.⁴ The International Contact Dermatitis Research Group developed a scoring system for assessing patch test reactions that were accepted by the North American Contact Dermatitis Group. However, this method is limited by its subjectivity and possible variability between observers.^{5,6}

TABLE 1 International contact dermatitis research group scoring system

Score/code	Interpretation	Advice
0	Negative reaction	
±	Doubtful reaction, faint erythema	Caution with interpretation, especially with less common allergens. Consider repeat testing or follow-up with ROAT testing.
1+	Weak (nonvesicular) positive reaction; erythema, infiltration and possibly papules, slight infiltration	Erythema should be palpable and occupy > 50 percent of patch test site.
2+	Strong (vesicular) positive reaction; erythema, infiltration, papules, and vesicles	Look for microvesicles to occupy at least 50 percent of the patch test site.
3+	Extreme positive reaction, bullous reaction, ulcerative	Confluent vesicles.
IR	Irritant reactions	There is a broad range. Mild irritant reactions have a glazed appearance. Moderate reactions are follicular (pustular in atotics). Extreme reactions can be ulcerative.

Different noninvasive modalities have been explored in attempts to find a more objective method of evaluating patch test reactions including bioengineering methods, laser Doppler flowmetry (LDF, measurement of cutaneous blood flow), colorimetry (assessment of erythema), IR thermography, and 20-MHz ultrasound A-scans.⁷ However, these methods were unable to gain significant traction in clinical practice and have yet to be established as appropriate objective methods for patch test reading.⁸

Optical coherence tomography (OCT) is an advanced imaging method which enables noninvasive in vivo visualization of skin layers such as the stratum corneum, the epidermis, the upper dermis, skin appendages, and blood vessels. In comparison with other non-invasive methods, OCT provides additional information on micro-morphological changes in ACD and holds promise as an objective method of grading patch test reactions.^{9,10}

Hence, in this pilot study we aim to investigate the micromorphological changes of ACD reactions and identify objective, quantitative in vivo OCT markers that correlate with clinically graded patch test reactions.

2 | METHODS

2.1 | Patients and patch testing

Patients with a clinical history of ACD underwent patch testing at the University of Miami Hospital, Dermatology outpatient clinic. Patch tests were placed on the upper back according to the International Contact Dermatitis Research Group and the North American Contact Dermatitis Group Guidelines and removed after 48 hours. Reaction sites were clinically graded 72 hours after patch placement (Table 1).¹¹ After obtaining written informed consent, areas with positive reactions were photographed and marked for OCT

evaluation. This study was approved by the Institutional Review Board at the University of Miami.

2.2 | OCT measurements

Optical coherence tomography measurements were obtained on both skin sites with positive reactions and control sites without positive reactions. A commercial OCT machine, VivoSight® (Michelson Diagnostics, Kent, UK), was used in this study with a central wavelength of 1305 nm; an optical resolution of <7.5 µm lateral and <5 µm axial; a scan area of 6 × 6 mm; and a penetration depth around 1-2 mm. The settings for all scans were 120 frames and 6 mm width and each scan took 30-90 seconds.

2.3 | Quantitative dynamic OCT scan analysis

Measurements of the dynamic or speckle variance signal were obtained using a software tool provided by the Michelson Diagnostics Ltd. Dynamic OCT signals were measured at depths of 0.1 and 0.35 mm from the skin surface. Any local movement, such as that produced by cutaneous capillary blood flow, is quantified by a dynamic OCT signal. By calculating the signal intensity of speckle variance across at frames at different depths, the software indirectly measured cutaneous capillary blood flow beneath the ACD and control reaction sites.¹²

2.4 | Quantitative OCT optical attenuation analysis

Optical attenuation analysis was performed using a software tool provided by Michelson Diagnostics Ltd. The software extracted the average OCT signal vs. depth profile across all data points in the 6 mm × 6 mm scan to generate an attenuation coefficient for a given

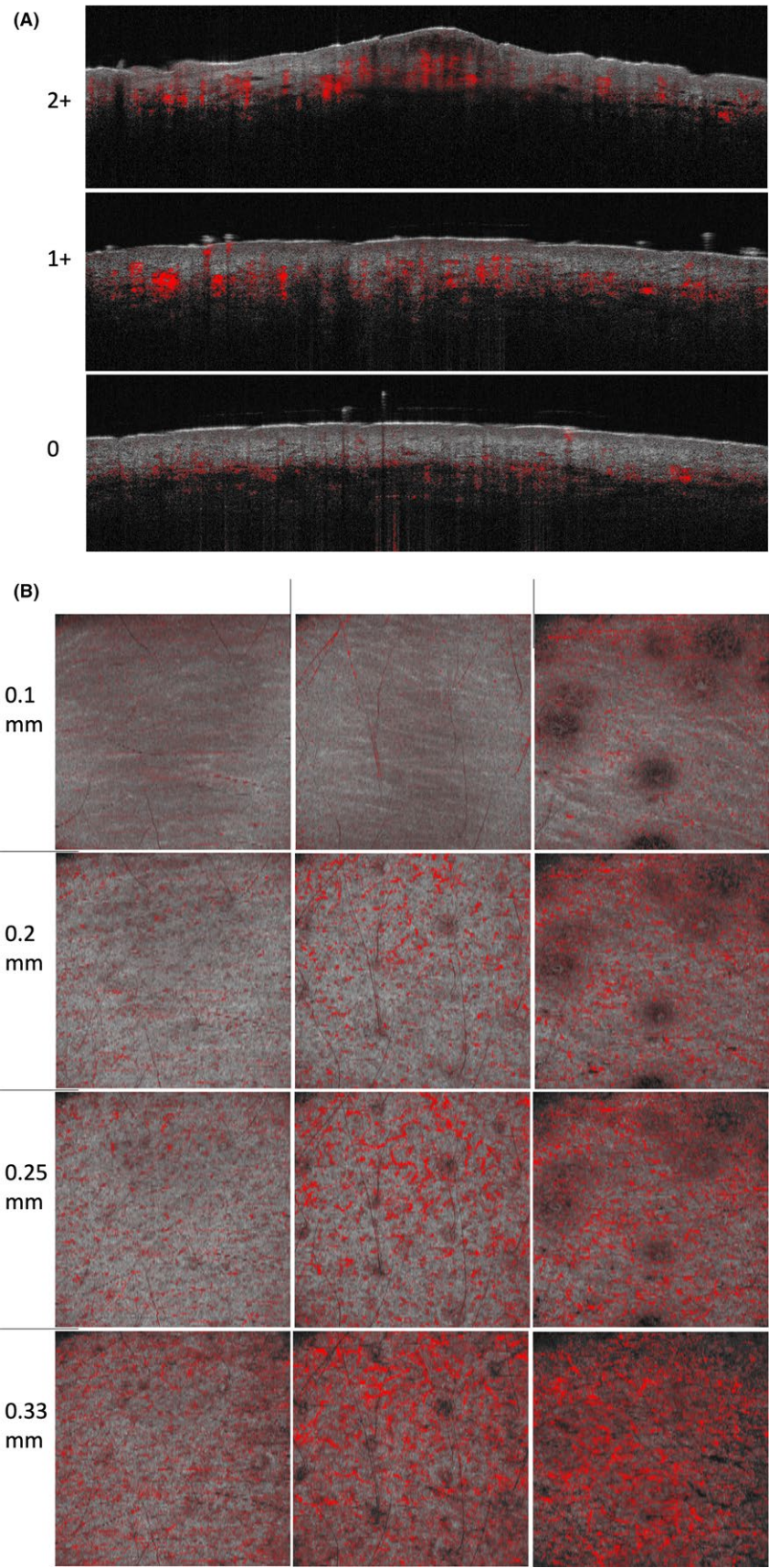


FIGURE 1 (A) Original cross-sectional OCT slice of cutaneous allergic reactions (0-2 +). (B) D-OCT *en face* images of the back of a subject with 2 positive allergic cutaneous reactions grades. 1 to 2 +

TABLE 2 Mean and standard deviation of blood flows and attenuation Coefficient in different clinical scoring of allergic patch test reactions. Correlation between clinical scoring of allergic patch test reactions and OCT measurements

Grade	Count	OCT measurements	Mean ± SD
0	7	Blood flow 0.1 mm	0.029 ± 0.033
		Blood flow 0.35 mm	0.053 ± 0.011
		Attenuation	2.58 ± 0.092
1+	4	Blood flow 0.1 mm	0.039 ± 0.044
		Blood flow 0.35 mm	0.078 ± 0.015
		Attenuation	2.96 ± 0.121
2+	14	Blood flow 0.1 mm	0.068 ± 0.024
		Blood flow 0.35 mm	0.121 ± 0.008
		Attenuation	3.05 ± 0.065
OCT measurements		P-value	
Blood flow 0.1 mm		0.6106	
Blood flow 0.35 mm		0.0002	
Attenuation coefficient		0.0016	

bold values shows the statistically significant differences

sample. The attenuation coefficient is a quantitative marker for entrance signal disruption.

2.5 | Statistical analysis

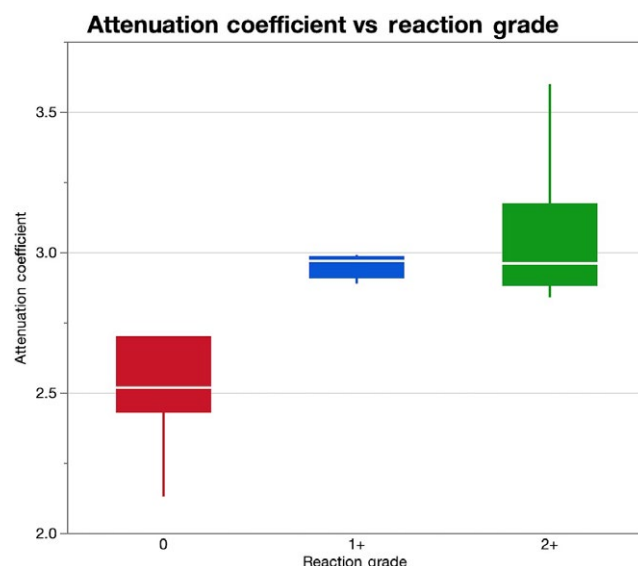
Continuous variables were calculated and listed by mean, standard deviation, and 95% confidence interval by total sample and by reaction grade. Blood flow at 0.1 mm, blood flow at 0.35 mm, and attenuation coefficients were compared across the three reaction grades using one-way ANOVA tests. Statistical significance was determined at the level of $\alpha < 0.05$. All statistical analyses were completed using JMP[®] Pro version 14.0.0 (SAS Institute Inc., Cary, NC).

3 | RESULTS

In total, 7 individuals (5 females, 2 males) with a positive patch test reaction to at least one allergen underwent OCT evaluation. Mean age of study participants was 54.4 ± 16.2 years. OCT measurements from 18 positive (grade 1+ and 2+) and 7 negative (grade 0) patch test reaction sites were obtained and analyzed.

Under OCT, we qualitatively observed an increase in epidermal thickness and density in grade 1+ and 2+ patch test allergic reactions. Moreover, well-demarcated signal-free cavities were visualized in all grade 2+ reactions (Figure 1).

Mean cutaneous blood flow rates at depths of 0.1 mm were 0.029 ± 0.033 mm/s, 0.039 ± 0.044 mm/s, and 0.068 ± 0.024 mm/s for reaction grades 0, 1+, and 2+, respectively (Table 2.). Reaction sites graded 1+ and 2+ had the highest measured flow, yet there was no significant difference across the three reaction grades ($P = 0.28$) at a depth of 0.1 mm. For cutaneous blood flow at 0.35 mm, mean flow rates were 0.053 ± 0.011 mm/s, 0.078 ± 0.015 mm/s, and 0.121 ± 0.008 mm/s for reaction grades 0, 1+, and 2+, respectively (Table 2). At a depth of 0.35 mm,

**FIGURE 2** Correlation between clinical scoring of allergic patch test reactions and attenuation coefficient

cutaneous blood flow monotonically increased with reaction grade severity and blood flow measurements significantly differed across the three reaction grades ($P < 0.01$). Moreover, attenuation coefficients significantly increased across the three reaction grades (2.58 ± 0.092 , 2.96 ± 0.121 , 3.05 ± 0.065 ; $P < 0.01$). (Table 2, Figures 2 and 3)

4 | DISCUSSION

Patch testing is the gold standard for evaluating suspected ACD and performing the test has been demonstrated to reduce the costs of treatment and improve quality of life.^{13,14} However,

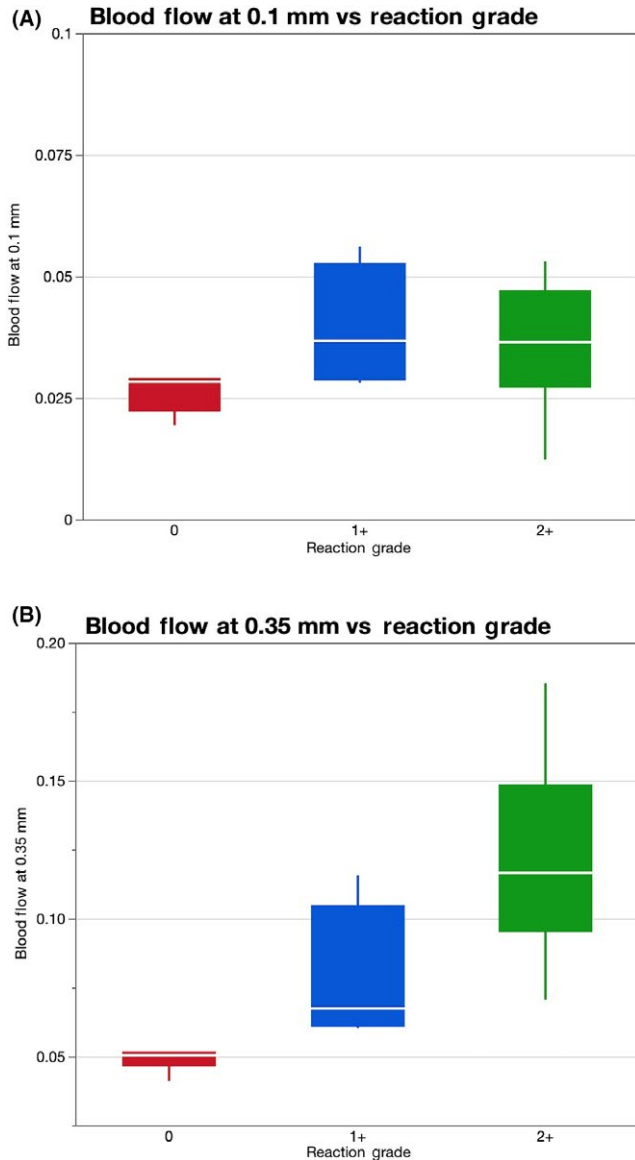


FIGURE 3 Correlation between clinical scoring of allergic patch test reactions and blood flow at depth of 0.1 mm and 0.35 mm

current methods to interpret patch tests are limited by the use of subjective techniques that may be inaccurate or insensitive.⁴ Moreover, noninvasive imaging technologies such as ultrasound may provide fairly undifferentiated information and be susceptible to the same limitations as clinical grading.^{6,15,16} OCT is a promising new modality for visualizing the micromorphological details of an ACD lesion and may offer an objective assessment of patch test reactions.

Gambichler et al previously evaluated ACD by using OCT and correlated the clinical grading of patch test reactions with OCT's findings. When compared to negative controls, they observed marked skin folds, disrupted entrance signals, and an increase in epidermal thickness.⁵ However, cutaneous blood flow changes over different clinical patch test grades were not studied.

In our study utilizing OCT, we confirmed that ACD tended to produce larger skin folds and increase epidermal thickness, particularly

in grade 2+ reactions. We theorize the marked skin folds observed in ACD may be attributed to intercellular edema and the hyperproliferative processes induced by locally released inflammatory cytokines.^{5,11} Additionally, under OCT we visualized well-demarcated signal-free cavities in grade 2+ ACD reactions. This finding likely corresponds to vesicle formation and coalescing spongiosis, a typical feature of grade 2+ and 3+ patch test reactions that distinguishes grade 2+ and 3+ reactions from less severe patch test grades (0 and 1+).¹⁷ However, micromorphological features such as cutaneous thickness and density can vary across people of different ethnicities and genders. Therefore, skin thickness and echogenicity of the upper dermis may be unreliable for differentiating patch test reaction grades.

As ACD reaction grades worsened in severity, attenuation coefficients and visualization depths significantly increased and decreased, respectively. This is an expected finding, given higher attenuation coefficients indicate a reduced penetration depth by the interrogating laser beam. As the cutaneous response to allergens includes interstitial edema, cellular infiltrates, and blood vessel dilatation, this edematous inflammation likely decreases the image penetration depth of OCT scans due to water's chromophoric properties in the infrared spectrum.¹⁸ Because attenuation coefficients significantly differed across patch test grades, this quantitative parameter may be of clinical value as an objective measure of ACD reaction grade.

Lastly, quantitative blood flow was analyzed among clinical responders at two predetermined depths. While mean differences in blood flow from baseline were statistically significant in grade 2+ reactions at both depths, superficial blood flow alterations at 0.1 mm did not statistically change across the clinical grades studied. Meanwhile, the greatest changes in blood flow were demonstrated at the depth of 0.35 mm and blood flow significantly increased with worsening reaction severity. Thus, in vivo OCT measurements of cutaneous blood flow at 0.35 mm may help differentiate between clinical patch test grades of 0, 1+, and 2+.

Altogether, these data suggest that attenuation coefficients and cutaneous blood flow at 0.35 mm may potentially serve as quantitative parameters for objective patch test grading. Incorporating OCT evaluation into patch test interpretation algorithms may offer more consistent and accurate allergic reaction grading. Furthermore, it may also improve the accessibility of patch testing. According to 2014 Centers for Medicare & Medicaid Services data, patch testing is nationally underutilized based on the estimated prevalence of ACD.¹⁹ The use of objective measures may reduce the learning curve for patch test interpretation and remove a barrier for clinics to offer the test in their practice. Overall, OCT evaluation in patch testing has the potential to improve diagnostic accuracy and better inform treatment recommendations.

4.1 | Study limitations

This study has inherent limitations that need to be considered. First, this pilot study is inherently limited by a small sample size and would benefit from additional patch test reactions. Second, our study

patients did not present with any grade 3+ patch test reactions, and thus, OCT variables were unable to be evaluated in the setting of all clinical reaction grades. Larger studies are needed to corroborate these findings and further define standard value ranges for attenuation coefficient and cutaneous blood flow across all clinical reaction grades.

5 | CONCLUSION

OCT findings in ACD include noticeable skin folding, entrance signal disruption (increased attenuation coefficient), the presence of demarcated signal-free cavities, and an increase in quantitative blood flow. Statistically significant changes in cutaneous blood flow were measured at the depth of 0.35 mm across the spectrum of clinical reaction grades observed. OCT may help dermatologists differentiate clinical scoring of ACD and thereby improve their diagnostic accuracy and interpretation of patch test reactions.

ORCID

Ali Rajabi-Estarabadi  <https://orcid.org/0000-0002-3631-9844>

Darren C. Tsang  <https://orcid.org/0000-0002-6409-7070>

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