

Dynamic optical coherence tomography of histamine induced wheals

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Abstract

Background: Dynamic optical coherence tomography (D-OCT) is a noninvasive imaging technique providing images of the skin and detecting movement in the tissue ie, measuring blood flow. The “attenuation coefficient” describes light absorption and scattering abilities of the tissue, while the dynamic signal provides a quantitative measure of the blood flow.

Aim: The study objective is to describe the dynamic changes of the skin and skin vessels during histamine release using D-OCT.

Methods: Healthy volunteers had local histamine injections in the skin and D-OCT-scans performed at 2-minute intervals to detect changes in blood flow, attenuation and clinical symptoms.

Results: 9/10 participants showed clinical wheals. An increase in blood flow was shown at all depths ($P < .001$ at 2 minutes). The highest relative increase was seen at 300 μm . The signal at 500 μm decreased to insignificant values and remained low after 4 minutes. A decrease in visualization depth of up to 32.7% as well as a significant increase in the attenuation coefficient was shown ($P < .001$ at 12 minutes for both tests).

Conclusion: Dynamic optical coherence tomography is able to reliably identify changes in blood flow of histamine induced wheals. Dermal oedema reduces visualization depth and increases the attenuation coefficient.

KEYWORDS

imaging, inflammation, microvasculature, optical coherence tomography

1 | INTRODUCTION

Optical coherence tomography (OCT) provides in vivo cross-sectional and *en face* images of the skin. Images are based on interferometry of infrared light, and appear as cross sectional B-scans. By recording several laterally shifted B-scans, it is possible to create horizontal *en face* images.¹ The first OCT study of human skin was published in 1997.² Since then, technological advances have allowed for an improved penetration depth and higher resolution¹ as well as supplementary functional information eg, on blood vessels. *Dynamic* OCT (D-OCT) is based on detection of changes in *speckles* in the scanned

tissue enabling measurement of movement of eg, red blood cells and can therefore be used for identifying cutaneous blood vessels³ as seen in Figure 1. Studies on D-OCT have mainly focused on describing morphological vascular features for specific diseases, including psoriasis,⁴ acne,⁵ connective tissue disease⁶ and non-melanoma skin cancer.⁷

An indirect quantitative blood flow measurement with D-OCT can be demonstrated by measuring the average speckle variance signal across all B-scan frames at different depths in order to assess the blood flow at different skin depths.⁸ With this quantitative method, D-OCT is able to reliably measure physiological

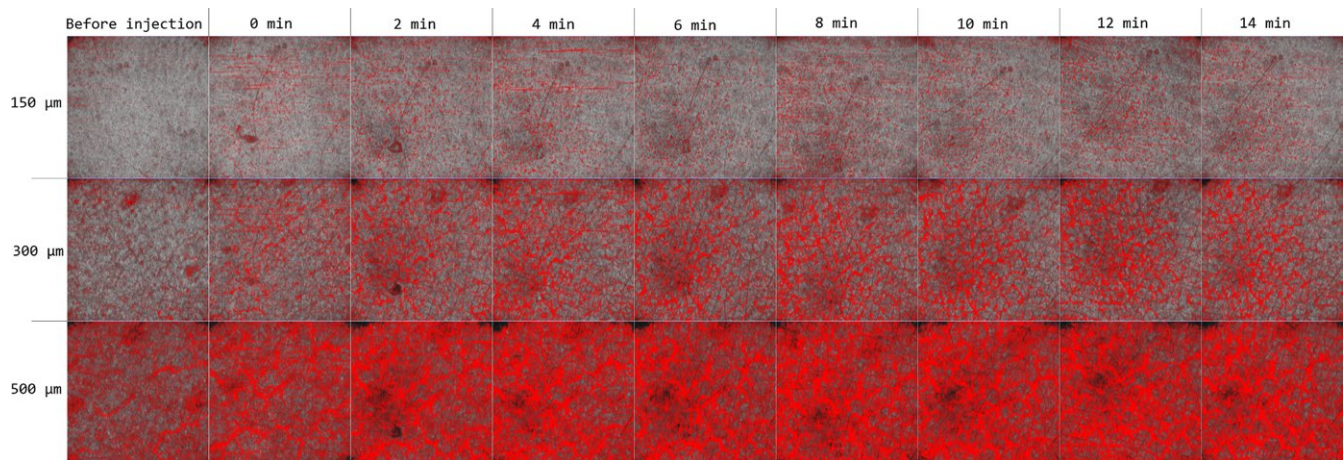


FIGURE 1 6×6 mm D-OCT *en face* images of the forearm of a participant during the study. At 150 μm , the blood flow is slowly increasing, with no definite plateau level, while the blood flow reached plateau level in 4 min at 300 μm and in 2 min regarding 500 μm . In contrast with Table 2, the blood flow signal does not seem to decrease at 500 μm after 4 min [Colour figure can be viewed at wileyonlinelibrary.com]

changes in the blood flow of the skin with a significant positive correlation with other blood flow measurement techniques.⁹

Optical coherence tomography has also been used for quantifying the optical properties of tissue in terms of its effect on incident light via the mechanisms of absorption and scattering. The image penetration depth in the tissue is a basic measure of its optical properties at the OCT wavelength. The rate of decrease in OCT signal intensity with depth quantifies how strongly the tissue absorbs and scatters the incident light and is closely related to this. The *optical attenuation coefficient* α , measures the rate of decrease and can be extracted from the OCT image data. OCT-derived optical attenuation has been used to classify tissue types, differentiate between healthy and cancerous tissue,^{10–12} and to measure burn scars and wound healing.¹³

Inflammation is known to affect the image quality and penetration depth.¹⁴ It may therefore be hypothesized that the optical attenuation coefficient α is affected by fluid changes in the tissue such as oedema and an increased volume of blood per unit volume, resulting in more absorption and therefore higher α . The acute inflammatory response of urticaria causes oedema of the dermis. Water is a chromophore able to absorb and scatter light in the infrared spectrum,¹⁵ therefore it can be hypothesized that inflammation may decrease the visualization depth of OCT due to light scattering and absorption. The objective of this study is to describe the dynamic changes of the skin and skin vessels during histamine release using OCT imaging. In addition to this methodological point, the study has broader clinimetric relevance as various inflammatory skin diseases such as atopic dermatitis and chronic urticaria are diagnosed on a clinical basis. No quantifiable measure of the treatment effect is available, why a reliable tool for doing that may add value in the diagnostics and treatment monitoring of this disease group.

2 | MATERIAL & METHODS

2.1 | Study population

Ten healthy volunteers >18 years of age, five of each gender with no history of allergies and no current pregnancy or breastfeeding, were included after signing informed consent.

2.2 | OCT-scan procedure and histamine injection

Prior to injection, an area in the middle of the volar side of the right forearm was marked with surgical pen. OCT-scanning of the marked area was performed to establish a baseline before intervention. The healthy volunteers were then injected in the marked area with 0.02 mL of histamine corresponding to 0.0001 mg, using a syringe (Omnifix®-F Solo 1 mL fine dosage syringe with a 30G needle). Afterwards, OCT-scans were performed immediately after and in 2-minute intervals the following 14 minutes.

In this study, we used the commercially available Vivosight Dx (Michelson Diagnostics, Kent, UK) 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 mm. The settings for all scans were 120 frames and 6 mm width.

2.3 | Quantitative D-OCT-scan analysis

Quantitative analyses of the D-OCT scans were performed in order to get a measure of the *dynamic* or *speckle variance* signal using a software tool provided by the producer. A *Dynamic* OCT signal indicates that local motion is detected, such as that caused by blood flowing in an imaged blood vessel, contrasting with *static* in which no motion is detected. The tool provides an indirect measure of blood flow in the D-OCT-scans by calculating the signal intensity of speckle variance across all frames at different

TABLE 1 Table 1 contains the descriptive statistics of the different outcome variables

	N = 10
Gender, male/female	5/5
Clinical response, responders/total	9/10
Age, median (IQR)	36.5 y (22.5)
Baseline flow 150 μm , median (IQR)	0.0269 (0.040)
Baseline flow 300 μm , median (IQR)	0.1100 (0.050)
Baseline flow 500 μm , median (IQR)	0.2761 (0.067)
Max flow 150 μm , median (IQR)	0.1121 (0.082)
Max flow 300 μm , median (IQR)	0.3047 (0.124)
Max flow 500 μm , median (IQR)	0.4092 (0.125)
Visualization depth baseline, median (IQR)	0.725 mm (0.13)
Visualization depth minimum, median (IQR)	0.520 mm (0.23)
Attenuation at baseline, median (IQR)	1.849 (0.45)
Attenuation maximum, median (IQR)	2.333 (0.85)

depths, providing an arbitrary measure of blood flow that corresponds to the proportion of image pixels in which movement is detected; thus a D-OCT result of 1.000 indicates that 100% of pixels at that depth in the OCT images exhibited motion. The method has been utilized in previous studies on D-OCT.⁸

2.4 | Quantitative OCT optical attenuation analysis and measurement of visualization depth

A software tool provided by Michelson Diagnostics Ltd was used to perform optical attenuation analysis. This tool extracts the average OCT signal vs depth profile across all data points in the 6 mm $\times$ 6 mm scan and then obtains the gradient, to return the optical attenuation coefficient α . The visualization depth is an observer's estimate of the distance threshold from the skin surface in which skin structures are still visible.

2.5 | Statistical analysis

All statistical testing was performed using IBM SPSS Statistics 24 (IBM, Armonk, NY, USA), and all tables and graphs were drawn using Excel (Microsoft office 2013, Microsoft Corporation, Redmond, WA, USA). For statistical tests, we used paired samples *t* test for parametric testing of changes in blood flow, attenuation and visualization depth with Holm-Bonferroni correction for multiple testing, α -level 0.05.

3 | RESULTS

We included 10 healthy volunteers, five men and five women with a median age of 36.5 years (range 22-61). After histamine

injection 9/10 volunteers developed a clinical response with hives at the injection site. The participant with no clinical response was excluded from further data analysis (see Table 1 for further descriptive statistics). We conducted paired samples *t* tests for changes in blood flow, measurement depth, and attenuation coefficients shown in Table 2. The Holm-Bonferroni correction was calculated based on each type of measurement, leaving 8 ranks for attenuation and visualization depth and 24 ranks for blood flow measurement. Significant paired samples *t* tests after Holm-Bonferroni correction are marked with * in Table 2. Here, we can see a significant decrease in visualization depth and a significant increase in attenuation and blood flow at the 150 μm depth from 2 minutes onwards. The blood flow at 300 and 500 μm is significantly increased immediately after injection, though the blood flow at 500 μm depth decreases again to insignificant values after 4 minutes. Figure 1 shows OCT-images of the development in blood flow during the study. Figure 2 shows the mean blood flow at 150, 300, and 500 μm with 95% CI. The fractional decrease in visualization depth was: 2.5%_{0min}, 10.7%_{2min}, 22.4%_{4min}, 26.1%_{6min}, 28.0%_{8min}, 28.8%_{10min}, 32.7%_{12min}, and 32.4%_{14min}.

4 | DISCUSSION

Histamine has various physiological functions in the body including the recruitment of an acute inflammatory response via activation of the H1-receptor.^{16,17} The usual clinical presentation of urticaria consists of intensely pruritic wheals and oedema of the subcutaneous or interstitial tissues. Light and electron microscopy of drug induced urticarial skin reveals perivascular lymphatic infiltrates, mild vascular dilation, dermal oedema, and degranulated mast cells.¹⁸

Following the injection of histamine, the attenuation coefficients and visualization depths showed a significant increase and decrease, respectively, at 2 minutes and onwards, as seen in Figure 3. The difference increased over time showing the highest values at 6 minutes and onwards regarding attenuation. Regarding visualization depths, the biggest decreases of >0.1 mm or >22% were seen at 4 minutes and later. This implies a negative correlation between attenuation coefficient and visualization depth, as would be expected, because a higher attenuation coefficient indicates reduced penetration depth by the interrogating laser beam. The cutaneous physiological response to injected histamine is dermal oedema,¹⁸ and the findings therefore suggest that the oedema in the inflammatory tissue decreases the image penetration depth of OCT-scans most likely due to water's function as a chromophore, especially in the infrared spectrum.¹⁵

The quantitative blood flow was analysed among clinical responders at three predetermined depths of 150, 300 and 500 μm . The mean difference in blood flow from baseline showed significant differences at each depth (See Figure 2 and Table 2). The greatest changes in blood flow is shown at 300 μm with the highest λ -values of 0.145-0.196 at plateau level after 4 minutes. The absolute

TABLE 2 Paired samples *t* tests of visualization depths, attenuation coefficients and blood flow at 150, 300 and 500 μ m depth. All *P*-values that are significant after Holm-Bonferroni correction are marked with *

	Visualization depth			Attenuation coefficient			Blood flow 150 μ m			Blood flow 300 μ m			Blood flow 500 μ m		
	λ -value (95% CI), mm	<i>P</i> -value	λ -value (95% CI)	<i>P</i> -value	λ -value (95% CI)	<i>P</i> -value	λ -value (95% CI)	<i>P</i> -value	λ -value (95% CI)	<i>P</i> -value	λ -value (95% CI)	<i>P</i> -value	λ -value (95% CI)	<i>P</i> -value	λ -value (95% CI)
0 minutes	-0.018 (-0.055, 0.019)	.300	0.118 (-0.115, 0.350)	.276	0.035 (0.009, 0.061)	.014	0.081 (0.062, 0.099)	<.001*	0.087 (0.051, 0.122)	<.001*	0.129 (0.078, 0.122)	<.001*	0.116 (0.040, 0.192)	.008	0.091 (0.000, 0.183)
2 minutes	-0.071 (-0.119, -0.024)	.009*	0.168 (0.049, 0.287)	.011*	0.055 (0.036, 0.073)	<.001*	0.145 (0.144, 0.176)	<.001*	0.129 (0.078, 0.122)	<.001*	0.129 (0.078, 0.122)	<.001*	0.116 (0.040, 0.192)	.008	0.091 (0.000, 0.183)
4 minutes	-0.133 (-0.202, -0.064)	.002*	0.325 (0.072, 0.578)	.018*	0.063 (0.035, 0.073)	<.001*	0.177 (0.137, 0.217)	<.001*	0.116 (0.040, 0.192)	<.001*	0.116 (0.040, 0.192)	<.001*	0.116 (0.040, 0.192)	.008	0.091 (0.000, 0.183)
6 minutes	-0.152 (-0.216, -0.088)	<.001*	0.497 (0.192, 0.802)	.006*	0.062 (0.029, 0.096)	.003*	0.168 (0.122, 0.215)	<.001*	0.091 (0.000, 0.183)	<.001*	0.091 (0.000, 0.183)	<.001*	0.091 (0.000, 0.183)	.050	0.091 (0.000, 0.183)
8 minutes	-0.161 (-0.240, -0.083)	<.001*	0.517 (0.266, 0.768)	<.001*	0.076 (0.043, 0.109)	<.001*	0.196 (0.143, 0.250)	<.001*	0.099 (0.003, 0.194)	<.001*	0.099 (0.003, 0.194)	<.001*	0.099 (0.003, 0.194)	.045	0.099 (0.003, 0.194)
10 minutes	-0.164 (-0.245, -0.084)	.002*	0.550 (0.321, 0.778)	<.001*	0.066 (0.031, 0.100)	.002*	0.189 (0.141, 0.237)	<.001*	0.094 (0.001, 0.188)	<.001*	0.094 (0.001, 0.188)	<.001*	0.094 (0.001, 0.188)	.048	0.094 (0.001, 0.188)
12 minutes	-0.181 (-0.0251, -0.111)	<.001*	0.475 (0.253, 0.698)	<.001*	0.082 (0.041, 0.123)	.002*	0.197 (0.148, 0.247)	<.001*	0.090 (-0.010, 0.190)	<.001*	0.090 (-0.010, 0.190)	<.001*	0.090 (-0.010, 0.190)	.073	0.090 (-0.010, 0.190)
14 minutes	-0.180 (-0.257, -0.103)	<.001*	0.621 (0.273, 0.969)	.003*	0.066 (0.028, 0.104)	.004*	0.184 (0.132, 0.236)	<.001*	0.083 (-0.019, 0.185)	<.001*	0.083 (-0.019, 0.185)	<.001*	0.083 (-0.019, 0.185)	.099	0.083 (-0.019, 0.185)

measure of blood flow is highest at 500 μ m, though a smaller change is recorded with a peak value of 0.129 at 2 minutes. At 500 μ m the measured blood flow also decreases to insignificant mean differences after 4 minutes. It is speculated that the observed decrease in blood flow is due to an increase in optical attenuation causing OCT signal roll-off at 500 μ m depth. The blood flow at 150 μ m showed a significant increase after 4 minutes and throughout the observation period though with a lower slope than 300 and 500 μ m. The increase in blood flow supports our hypothesis of dermal oedema in acute inflammation causing the decreased visualization depth. Former studies of the effect of injected histamine on blood flow using laser Doppler instead of D-OCT showed a similar correlation between the development in blood flow and wheals.¹⁹

The data may alternatively be interpreted as a potential method of objectively quantifying oedema. This may be hypothesized to further improve the reproducibility and objective classification of patch test scoring.²⁰ Method-OCT may, however, not be applicable in a clinical setting for as the utility of clinical scores is high, but it may be useful in an experimental setting.

Quantification of wheal reactions and cutaneous blood flow has been studied by other means than OCT. Laser Doppler flowmetry (LDF) uses Doppler-shifted frequencies from back scattered laser from moving blood cells. The signal-noise ratio from LDF is proportional to velocity of blood flow, and has shown to be able to identify an increase in signal from central parts of wheals during a reaction, but was only able to differentiate different concentrations of histamine injected at the perilesional flare at not the centre of the lesion. The study also showed that recordings after 5-10 minutes were most accurate in differentiating flowmetry of different histamine solutions.²¹ These findings confirm, that the inflammatory response following skin exposed to histamine is best observed early during the inflammatory response, suggesting the following oedema to reduce the light penetration depth. Laser Doppler imaging (LDI) can be compared to LDF record skin perfusion in larger areas of up to 12 $\times$ 12 cm with a spatial resolution of 2 $\times$ 2 mm.²² A recent study suggests that LDF has no advantage in grading dermal inflammatory reactions compared to LDI.²³ During a wheal reaction it has been shown that clinical photography with enhanced colour differences is more sensitive in detecting differences compared to ordinary photographs using colour quantification software. A peak in red colour is found after 8 minutes followed by a rapid decrease in red colour.²⁴ Compared to our data in which the superficial vessels at 150 and 300 μ m show a rapid increase in blood flow from baseline to 8 minutes, it may be implied, that the flare of histamine induced wheals reaches peak value after $\approx$ 8 minutes. The broadest field of view for investigating inflammation can be achieved by thermography. Stüttgen found that deep urticarial lesions were associated with increased heat radiation while more superficial lesions had the contrary effect.²⁵ In agreement with this observation, high-resolution thermography has also been shown to reveal sub clinical lesions of tungiasis in dark skinned individuals by identifying a rise in local skin temperature,²⁶ however, the method has the shortcoming of delivering no actual

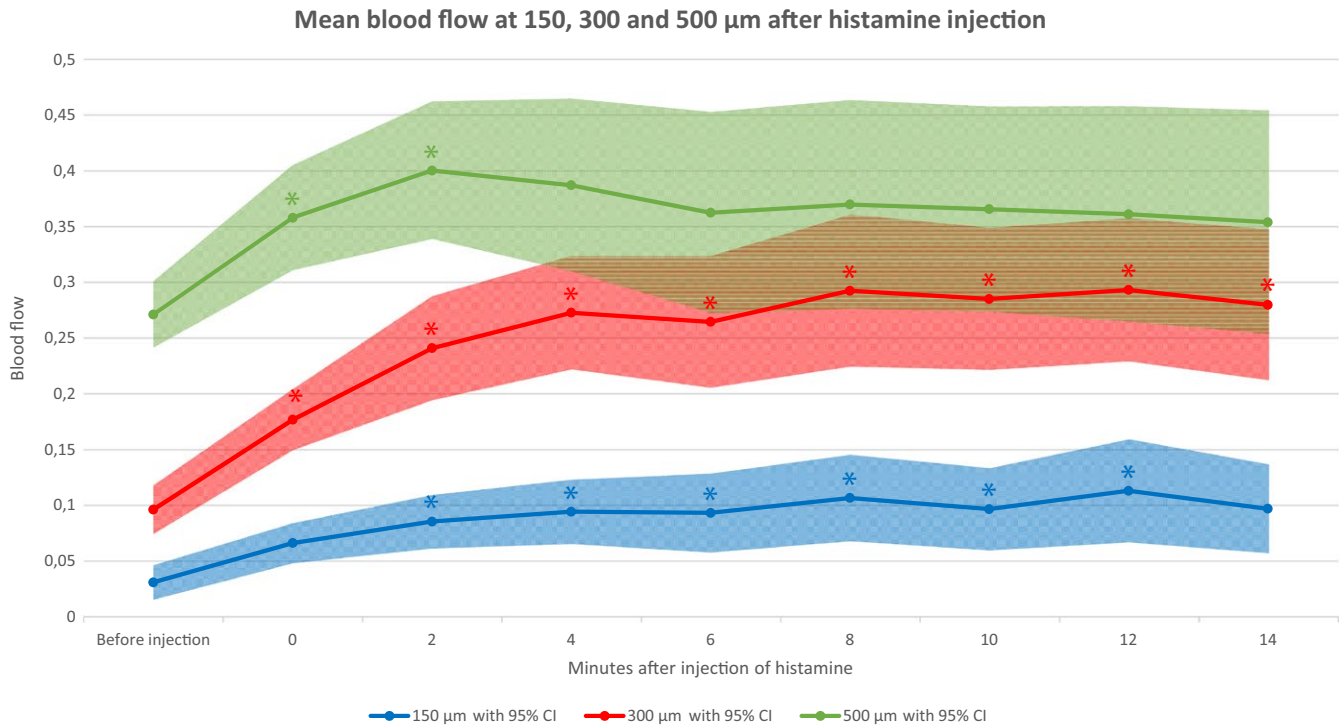


FIGURE 2 Mean blood flow at 150, 300 and 500 μm with 95% confidence intervals. The mean blood flow values that significantly differ from baseline (tested with paired samples *t* test and Holm-Bonferroni correction) are marked with *. See Tables 1 and 2 for more information [Colour figure can be viewed at wileyonlinelibrary.com]

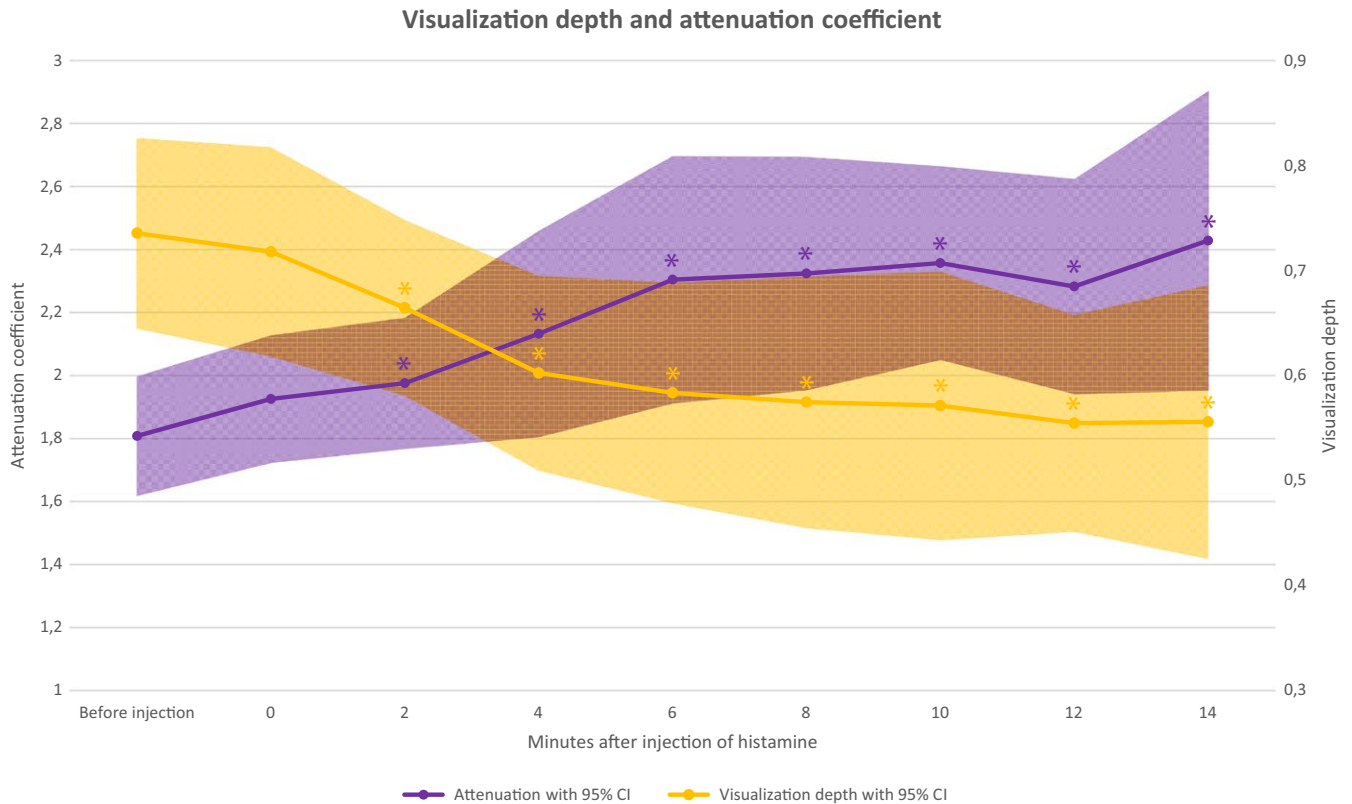


FIGURE 3 Mean attenuation coefficient and visualization depth with 95% confidence intervals. The mean values that significantly differ from baseline (tested with paired samples *t* test and Holm-Bonferroni correction) are marked with *. See Tables 1 and 2 for more information [Colour figure can be viewed at wileyonlinelibrary.com]

depth measurement in the summary surface scan. In contrast, depth measuring is generously provided by high frequency ultrasound (HFUS) which was applied in quantifying the thickness and tangential area, showing that thickness and diameter of wheal diameter increased up to 1.78 mm (SD ± 0.25) and diameter 6.08 mm (SD ± 0.73) at higher histamine concentrations.²⁷ This finding suggest that HFUS may be superior to OCT in evaluating the oedema of wheal reactions due to the limited penetration depth and field of view of OCT of ≈ 1 mm and 6×6 mm, respectively, however, OCT also provides the attenuation coefficient which may be a surrogate measure of the degree of oedema.

The study has limitations regarding the induction of the wheal and penetration depth. Wheals were induced using histamine injections with a needle and syringe instead of a simple lancet in order to better standardize the histamine dosage. Consequently, there is a higher precision regarding the delivered dose but a lower precision regarding the depth of delivery. D-OCT for the study of the cutaneous vasculature is limited by its penetration depth. In any pathology originating at depths of >500 μm , D-OCT would most likely have a low sensitivity. We are therefore not able to study vascular plexuses of the dermis, which are situated 1–1.5 mm from the skin surface, while the dermal papillary loops are visible in D-OCT.²⁸ It may therefore be hypothesized that if an injection was performed too deep in the skin, neither clinical nor OCT response would be recorded due to the low dose of histamine used. The use of D-OCT has benefits and limitations compared to LDF, only being able to quantify the speckle variance signal and not the velocity of moving blood cells like LDF and LDI.²¹ On the other hand, D-OCT is able to differentiate changes in blood flow at different depths and also provides structural and quantifiable information from the tissue not related to blood flow. The scan area of OCT is surpassed by LDI, while the field of view in LDI is much greater with 12×12 cm compared to 6×6 mm for OCT.

In conclusion, we have demonstrated that D-OCT is able to reliably identify changes in blood flow in histamine-induced wheals, and that histamine induced dermal oedema reduces visualization depth in OCT imaging of skin due to increased optical attenuation. At 500 μm depth, the increase in optical attenuation may affect the accuracy of the D-OCT measurement of blood flow, although vascular morphology can still be reliably identified. The ideal depth for evaluating the dynamic change in inflammatory skin diseases using OCT is suggested to be around 300 μm at which level the greatest and most significant increase in blood flow can be measured, while still being within the range of visualization with D-OCT. Our findings also suggest that D-OCT may be applicable in inflammation evaluation eg, patch testing in an experimental setting.

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