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***In vivo* volumetric imaging of microcirculation within human skin under psoriatic conditions using optical microangiography**

Jia Qin¹, Jingying Jiang^{1,2}, Lin An¹, Daniel Gareau¹, and Ruikang K. Wang^{1,3,*}

¹Department of Biomedical Engineering, School of Medicine, Oregon Health and Science University, 3303 SW Bond Avenue, Portland, OR 97239, USA

²College of Precision Instruments and Optoelectronics Engineering, Tianjin University, Tianjin 300072, P.R. China

³Department of Anesthesiology & Peri-operative Medicine. Oregon Health and Science University, 3181 S.W. Sam Jackson Park Rd., Portland, Oregon 97239, USA

Abstract

Background and Objective—There is a growing body of evidence suggesting that vascular abnormalities may play crucial role in several dermatologic diseases, such as psoriasis, port wine stain and skin cancer. To improve our understanding of vascular involvement in these skin conditions, there is a need for a non-invasive imaging modality capable of assessing 3D microcirculations within skin tissue beds *in vivo*. This study aims to demonstrate whether ultrahigh sensitive optical microangiography (UHS-OMAG) is feasible to visualize skin microcirculations in 3D and to quantify microvascular vessel density under normal and psoriatic conditions *in vivo*.

Study Design/Material and Methods—An UHS-OMAG system operating at 1310nm wavelength was used for *in vivo* imaging of microcirculation in human skin. The system has a spatial resolution of ~10 μm $\times$ 20 μm (axial $\times$ lateral), running at 280 frames per second to acquire 3D imaging dataset to represent morphology and capillary level microvascular blood perfusion within the scanned skin tissue volume. The sensitivity of the system to the blood flow is as low as ~4 $\mu\text{m/s}$. With this system, we performed the imaging experiments on the skin of a volunteer with stable plaque-type psoriasis. The microcirculation and structural information of normal and diseased skins were compared both qualitatively and quantitatively.

Results—The UHS-OMAG is capable of differentiating the microcirculation within the normal skins from that in the psoriatic skins. The 3D optical images show the blood vessel elongation and the dense network in the psoriatic lesion skin, the appearance of which is not observed within the normal skin. Based on the results obtained from one subject, the statistical analyses show that higher blood vessel density presented within the psoriasis lesion skin than that of the normal skin.

Conclusions—UHS-OMAG can be a valuable tool for imaging skin microcirculations non-invasively with high speed and high sensitivity, and therefore may have a useful role in future clinical diagnosis and treatment of dermatologic diseases such as psoriasis in human subjects.

Keywords

Non-invasive optical imaging; optical microangiography; microcirculation; psoriasis; blood vessel density

*Corresponding author: Ruikang K. Wang, Ph.D., Department of Biomedical Engineering, Biophotonics and Imaging Laboratory, Oregon Health & Science University, 3303 SW Bond Avenue, Portland, OR 97239, USA. wangr@ohsu.edu, FAX: 503-418 9317, Voice: 503-418 9311.

INTRODUCTION

Psoriasis is a chronic, inflammatory skin condition that affects approximately 2% of the population in western countries [1]. Previous studies showed the prominence of dermal microvascular expansion in lesion skin and suggested that psoriasis is angiogenesis-dependent [2]. To aid the clinical diagnosis and treatment of such skin conditions, there is a need for a non invasive imaging means to assess the blood circulation conditions within the tissue beds of human skin. Ideally, the imaging tool should be of high resolution and high sensitivity to the blood flow so that the capillary vessels can be resolved within human skin.

Currently, there are several technical methods available for imaging the blood vessels within human skin *in vivo*. Capillaroscopy and videocapillaroscopy [3–5] are the most reliable ways to perform microvascular analyses. However, these methods are only capable of providing capillary morphology within a very superficial layer ($<100\ \mu\text{m}$). Laser-Doppler perfusion imaging (LDI) and dynamic laser speckle imaging (LSI) techniques [6–8] are other noninvasive methods widely used to evaluate the vascular abnormalities in dermatology. Both LDI and LSI methods are based on Doppler effects generated by the light backscattered from the moving particles (e.g., red blood cells) in patent vessels; and they can provide real-time two dimensional perfusion maps of skin with high temporal resolution [9]. However, all aforementioned methods are not capable of providing depth-resolved perfusion maps of microvascular blood flow, which is needed for accurate assessment of the microcirculations under the diseased skin conditions.

Photoacoustic microscopy [10–12] is an emerging technique capable of extracting microvascular information with high penetration depth ($>1\ \text{mm}$). Based on the endogenous absorption effect of hemoglobin within the range of 500–600 nm, this method has been reported to provide volumetric blood vessel information noninvasively [12]. Unfortunately, it has relatively low spatial resolution ($>\sim 50\ \mu\text{m}$) for imaging microcirculations within human skin, which resolution is not sufficient to visualize capillary vessels.

Based on the mechanisms of light scattering, optical coherence tomography (OCT) is a promising imaging technique that is able to provide noninvasive 3D imaging of biological tissues with high resolution and high sensitivity [13,14]. By evaluating phase differences between adjacent A-lines in an OCT B-scan frame, a functional extension of OCT, phase-resolved Doppler OCT (PRDOCT) [15], is developed to extract velocity information of blood flow in functional vessels within the scanned tissue beds. More specifically, PRDOCT has been used to image the cerebral blood flow [16], blood flow phantoms [17,18], and heart of a rodent model [19]. Although the PRDOCT method is of high resolution and high sensitivity to the blood flow, its imaging performance is greatly deteriorated by at least two factors: 1) characteristic texture pattern artifact, which is caused by optical heterogeneity of the sample [20], and 2) phase instability that is caused by the sample motion artifacts [21].

Being a recent extension of OCT, optical micro-angiography (OMAG) [22] is an imaging technique capable of producing 3D images of dynamic blood perfusion within micro-circulatory tissue beds with an imaging depth of $\sim 2\ \text{mm}$. OMAG is a label-free technique because it uses the endogenous light scattering from flowing blood cells within patent vessels to produce the imaging contrast. An unprecedented sensitivity to the blood flow down to $4\ \mu\text{m/s}$ was reported with the most recent development of ultrahigh sensitive OMAG (UHS-OMAG) [23]. With such high sensitivity to the flow, the modality has been successfully employed to image the microcirculations within cortical brain in mice [24] and within human skin [23] and human retina [21,25,26]. The primary objective of this article is to demonstrate the utility of the UHS-OMAG in assessing subcutaneous vasculatures within

normal and diseased skin tissue beds *in vivo*. We select a stable psoriasis plaque for the current study. We show that UHS-OMAG is capable of differentiating the micro-vessel network within the psoriatic skin lesions from that in the normal skins. The promising results demonstrate the usefulness of the UHS-OMAG imaging modality in providing meaningful diagnostic information for skin diseases, such as psoriasis.

MATERIALS AND METHODS

Psoriasis subjects

All the measurements were performed on a young male volunteer with a stable psoriasis plaque located at the antecubital region (the front region of the right elbow). The experimental procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2008 [27]. During imaging, the volunteer was comfortably seated, with the forearm positioned under the optical imaging probe (see below). Figure 1 gives a photograph taken from the subject, showing the normal skin and lesion skin areas examined by the UHS-OMAG system. The skin region appearing reddish, indicated by the white arrow, is the psoriasis lesion skin. The tested area (marked by red square 2) was randomly selected and covered a surface area of $\sim 2 \text{ mm} \times 2 \text{ mm}$ on the lesion skin. A normal skin area of $\sim 2 \text{ mm} \times 2 \text{ mm}$ (marked by the yellow square 1) was also randomly selected near the lesion region. The selected areas for imaging were close enough to provide fair comparison between the two types of subcutaneous vasculature.

Experimental system setup

The schematic of the imaging system setup is shown in Fig. 2, which is similar to the one reported in [23]. Briefly, the system was illuminated by a superluminescent diode light source with a central wavelength of 1310 nm and a bandwidth of 65 nm that yielded an axial resolution of $\sim 10 \text{ } \mu\text{m}$ in air. The light from the light source was divided into two paths through a 2×2 optical coupler, one for the reference arm and the other for the sample arm. In the sample arm, the light was coupled into a custom-designed optical probe, containing a collimator, a pair of galvo mirrors and an objective lens with 30 mm focal length. This design of the optical probe provided a $\sim 20 \text{ } \mu\text{m}$ lateral resolution. The light backscattered from the sample and reflected from the reference mirror was routed back to the 2×2 coupler, and then sent to a home-built spectrometer via an optical circulator for the detection of spectral interference signals (i.e., interferograms). The spectrometer had a designed spectral resolution of $\sim 0.141 \text{ nm}$, providing an imaging depth of $\sim 2.22 \text{ mm}$ into the sample (assuming the refractive of the skin is ~ 1.35). A high speed InGaAs line scan camera was used in the spectrometer to capture the interferograms at a recording speed of 47,000 A-lines per second. With this imaging speed, the system sensitivity was determined at 105 dB at the depth position of 0.5 mm. The light power of the beam incident upon the skin was $\sim 3 \text{ mW}$, which is below the safe occupational exposure level established by the American National Standards Institute (ANSI Z136.1) [28]. With these settings of system parameters, the system sensitivity to the blood flow was determined to be within a range from $4 \text{ } \mu\text{m/s}$ to 22.2 mm/s , which we expect would be sufficient to image the capillary blood vessels within the skin tissue beds. The imaging was performed with the optical probe situated $\sim 30 \text{ mm}$ above the skin of interest, i.e., the imaging was done through air without any contact to the subject.

Imaging protocols

Since UHS-OMAG system was able to pick up small-scale velocity changes, motion artifacts might be generated from involuntary movement. In this study to mitigate this problem, a new scanning protocol was introduced in order to achieve faster imaging speed than that was used in our previous work [23]. Briefly, a saw tooth waveform was used to

drive x-scanner (for fast B scan) and a step function waveform for the y-scanner (for 3D scan, or C scan). Along x-scanning direction, 128 A-lines were captured with a $\sim 15\ \mu\text{m}$ spatial interval between adjacent A-lines to achieve one B-scan cross-sectional image, which covered a range of $\sim 2\ \text{mm}$ on the skin. When the duty cycle for the rising side of the saw tooth wave-form was set at 75% in one cycle, the speed for B-scans was determined at 280 frames per second (fps). For the y-scanning direction, the 2 mm scan range was evenly divided into 200 steps with a $\sim 10\ \mu\text{m}$ spatial interval between them. In each step, five frames were captured and processed to extract one B-scan cross-sectional flow image by using a previous method [23]. The total time for acquiring each 3D data cube took only ~ 3.6 seconds, which is suitable for *in vivo* detection. Twenty different positions in total ($\sim 2\ \text{mm} \times 2\ \text{mm}$ for each) were randomly selected for UHS-OMAG imaging, ten of which from the areas bearing the psoriasis lesion skin and the other ten from the normal skin adjacent to the psoriasis lesion.

RESULTS

A schematic drawing of microcirculation within human skin is shown in Fig. 3 as a meaningful reference for the detailed analyses of the experimental results obtained from the UHS-OMAG. According to the standard histopathology [29,30], the dermal vasculature consists of two major horizontal vascular networks: the superficial papillary vascular plexus lying at the junction between the avascular epidermis and the vascularized dermis, and the deep reticular vascular plexus lying near the dermal/hypodermal interface in the dermis. The two plexuses are linked by the communicating blood vessels that are oriented perpendicular to the plexuses [29].

Extensive analyses were conducted on all the UHS-OMAG images, and the results were discussed in relation to the differences of blood vessels between the lesion and normal skins.

Cross-sectional images and representative volumetric images

Figures 4(a) and (c) show typical B-scan cross sectional structure images captured from the areas representing the normal and the lesion skins, respectively. The blood flow information was extracted and highlighted in Figs. 4(b) and (d) by the UHS-OMAG algorithm. An obvious characteristic is that the papillary vessels in the lesion skin [pointed by the red arrows in Fig. 4(d)] appear more abundant and much longer than those in the normal skin [pointed by yellow arrows in Fig. 4(b)]. The expanded superficial microvessels in psoriasis lesion lie in close proximity to the overlying avascular epidermis.

By combining together the cross-sectional flow images with the sequential structural images, volumetric visualization of tissue morphology and micro-vasculature can be made available for both the normal and lesion skin. Figures 5 (a) and (b) show the overlaid 3D view of normal skin and lesion skin, which demonstrate that papillary loops appear elongated in the psoriasis skin. Equally important, it can be seen from Fig. 5 that the blood vessel in the lesion skin is much denser than that in the normal skin.

Depth-resolved *en-face* images

Figure 6 illustrates the representative *en-face* images at different depth positions (each column for the same depth) extracted from the volumetric blood flow images of the normal skin (the upper row) and the psoriasis lesion skin (the lower row), respectively. From left to right, these columns correspond to the depth of $\sim 210\ \mu\text{m}$ [(a) and (f)], $\sim 340\ \mu\text{m}$ [(b) and (g)], $\sim 530\ \mu\text{m}$ [(c) and (h)], $\sim 720\ \mu\text{m}$ [(d) and (i)] and $\sim 870\ \mu\text{m}$ [(e) and (j)], respectively, along the depth direction from the skin tissue surface. By comparison, the microcirculation within the lesion skin demonstrates a totally different pattern from that within the normal

skin. From Fig. 6(a), no obvious blood vessel networks could be observed at ~210 μm depth within the normal skin, which indicates that this depth layer must belong to the epidermal layer since there is no blood vessel anatomically in the normal epidermal layer [30]. Unlike Fig. 6(a), Fig. 6(f) shows the dense bright spots of blood vessels that are the papillary loops at the junction between the epidermis and the dermis. This information implies that the epidermal layer of the lesion skin is thinner than that of the normal skin.

Figure 6 (b) shows the capillary loops at the depth of ~340 μm within the normal skin, with some representative papillary loops marked by 1. Those papillary loops lie horizontally through the papillary layer, connecting the dermal arterioles and venules by forming capillary loops in the papillary plexus. In the lesion skin, due to the elongation and the microvascular angiogenesis [2], the papillary vessels represented as bright spots [marked by 2 in (f) and 3 in (g)] in a relatively thicker depth region (~210–340 μm). Figures 6(c) and (h) show the superficial reticular perfusion maps from the normal and lesion skin at the same depth (~530 μm), respectively. Because of the angiogenesis, Figure 6(h) demonstrates that the blood vessel network in the lesion skin appears denser than that in the normal skin shown in Fig. 6(c). This angiogenesis aspect could also be directly visualized through comparing Figs. 6(d) and (e) with (i) and (j), representing the deeper reticular vessel networks within the normal and lesion skin at the same depth, respectively. The flying through movies (not shown) give more intuition regarding the different blood vasculature architecture at different depths for further comparison between the normal and the lesion skin.

Quantification and statistical analyses

The blood vessel density (*BVD*) was calculated as a quantitative metric for comparing the blood vessel patterns within normal and psoriatic skins. In this study, *BVD* was defined as the ratio of the blood vessels area (*BVA*) to the total area of the tissue slice, represented by the B-scan structure area (*SA*). Firstly, all B-scan images, including the blood flow images and the corresponding micro-structural images, were converted into binary images by setting a threshold value of 15 dB to eliminate the noise effect on the calculations. *BVA* and *SA* were then determined by the pixel numbers of binary image of blood flow and the corresponding structural image, respectively. Finally, the *BVD* value was calculated using the following equation:

$$BVD=BVA/SA \quad (1)$$

Twenty different regions of skin areas (each of ~2 mm×2 mm) were randomly selected and examined, ten from the psoriasis lesion skin and the other ten from the normal skin. All *BVD* values were calculated, generating two groups of *BVD* values: Group 1 from psoriasis lesion skin while Group 2 from the normal skin. Fifty *BVD* values were obtained from each group. One group was obtained by randomly selecting 50 *BVD* values from Group 1, and the other from Group 2. The results are shown in Fig. 7 by the histogram distribution of the *BVD* values. Shown are also the normal distribution bell-curves evaluated by fitting the experimental data to the normal distribution function. The horizontal axis denotes the *BVD* value while the vertical axis denotes the probability density. It can be seen that both the distributions of the *BVD* values from normal skin (blue bars) and lesion skin (red bars) approximately follow the normal distribution.

To statistically evaluate the difference of blood vessel density within the normal skin and the lesion skin, the null-hypothesis and alternative hypothesis were used. The null-hypothesis is H_0 : the mean value of *BVD* values obtained from the psoriasis lesion skin is not different from the mean value of *BVD* values from the normal skin. The alternative hypothesis is H_A :

the mean value of *BVD* values obtained from the psoriasis lesion skin is significantly larger than the mean value of *BVD* values from the normal skin. Student's *t* test was used to perform statistical analyses to elucidate the *BVD* differences between the two types of skin since the current dataset meets the following requirements: (1) there are only two groups of the *BVD* values, one for the normal skin and the other for the psoriasis lesion skin; (2) the population variance is unknown; (3) the random variables (blood vessel densities for each group) show normal distribution (see Fig. 7); (4) the sample size is relatively small. The test results show the significant differences between blood vessel densities in normal and psoriasis human skin with *p*-value, **P*, smaller than 0.001. Figure 8 shows the error bar graph of *BVD* values for the normal skin and psoriasis lesion skin. The blood vessel density of normal skin (0.3687 ± 0.0422) is significantly smaller than that of the psoriasis lesion skin (0.5286 ± 0.0603).

DISCUSSION

The imaging results from skin microcirculation reported here indicate that UHS-OMAG is capable of differentiating the blood vessel network within the normal skin from that in the psoriatic skin conditions. Cross sectional images (B-scan frames) and representative volumetric images can be used to visually assess the differences of microcirculation between the normal skin and the lesion skin (Figs. 4 and 5). The *en-face* images (Fig. 6, i.e., the x-y plane views at different depths) are useful to examine the changes of the blood vessel appearance within the psoriatic lesion skin. Here, we see that the elongated blood vessels and the high blood vessel density appear in the psoriatic skin, the appearance of which is not observed within the normal skin. Furthermore, the histogram-based analyses (Figs. 7 and 8) statistically demonstrated the significant difference of *BVD* between the normal skin and the psoriasis lesion skin. The experimental results agree well with those from the previous studies [30–32]. Ryan (1969) [30] demonstrated the microcirculation with categories ranging from atrophy to hypertrophy for the epidermal changes in psoriasis. He explicitly described capillary elongating process over time in the psoriatic plaque. Creamer (2002) [32] used light microscopy to investigate the skin. His study demonstrated the short lengths of microvessels in the superficial papillary dermis, and the dilated and elongated superficial capillaries in psoriatic lesion skins. This latter feature represents exaggerated tortuosity and coiling of the apical segment of the capillary loops, which has been confirmed by intravital capillaroscopic studies [33], as well as by the results reported in this study.

Comparatively, UHS-OMAG imaging modality has the depth resolved capability and is able to create the volumetric vascular images with high resolution and high sensitivity and without the use of any contrast agents. Such ability is useful in providing more detailed information about skin microcirculation. The promising results reported in this study show the potential application of UHS-OMAG in the diagnosis and treatment assessment of human skin diseases, including not only psoriasis but also other diseases such as skin cancers and port wine stain. Regarding the port wine stain, the histopathological analysis [34] shows a normal epidermis overlying an abnormal plexus of dilated blood vessels located at a layer in the upper dermis. The depth of port wine stain varies from 100 to 1000 μm , and blood vessel diameter ranges from 10 to 300 μm . Smoller and Rosen [35] reported the morphological evidence of abnormal vascular innervations in the skin of patients with port wine stains. They postulated that the progressive vascular dilatation in this condition is resulted from impaired neural control. In this case, the UHS-OMAG may have a useful role in imaging the abnormal plexus of dilated blood vessel layer located in the upper dermis, providing an ability to quantify the blood vessel densities.

CONCLUSIONS

We have demonstrated that the UHS-OMAG imaging system has adequate sensitivity and imaging speed to image the volumetric microcirculation within the human skin *in-vivo*. We have shown that the different depth 2D *en-face* images and 3D volume images afforded by the OMAG imaging datasets can be manipulated to directly examine in detail the appearance of the blood vessel networks under normal and diseased conditions. Based on the data obtained from one subject, the statistical analysis results showed that the blood vessel density in the psoriasis lesion skin has a statistically significant difference when compared to that in the normal skin. Therefore, we expect that the UHS-OMAG may have a great value in the future clinical diagnosis and treatment assessment in human skin.

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Fig. 1. Photograph shows the regions of interest selected for UHS-OMAG imaging. The yellow square indicates an area of the normal skin (1), and the red square of the psoriasis lesion (2).

Fig. 2. Schematic of UHS-OMAG system used in this study, where SLD denotes the superluminent diode; PC the polarization controller; CCD the charge-coupled device.

Fig. 3. Schematic of microcirculation network appearing within human skin, which structurally contains three layers marked as epidermis, dermis and hypodermis. The dermis consists of papillary layer and reticular layer.

Fig. 4. Typical OMAG B-scan images taken from the regions of interest. Representative B-scan structural and the corresponding blood flow images obtained from the normal skin area [(a) and (b)] and from the psoriasis lesion skin area [(c) and (d)], respectively. The yellow arrows in (b) and red arrows in (d) indicate some representative blood vessels.

Fig. 5. Representative volumetric structural images (x-y-z 3D) merged with microcirculations obtained from (a) the normal skin and (b) the psoriasis lesion skin by UHS-OMAG. The cube size is $2 \times 2 \times 2.2 \text{ mm}^3$.

Fig. 6.

Typical *en-face* images (x-y plane) at the different depths within the normal skin (the upper row) and the psoriatic skin (the lower row). Columns from left to right correspond to the depths of $\sim 210\ \mu\text{m}$ (a and f), $\sim 340\ \mu\text{m}$ (b and g), $\sim 530\ \mu\text{m}$ (c and h), $\sim 720\ \mu\text{m}$ (d and i), and $\sim 870\ \mu\text{m}$ (e and j) measured from the tissue surface. One representative region of papillary loops is denoted by number 1 within the normal skin. The typical elongated papillary loops [marked by number 2 in (f) and 3 in (g)] are seen abundant but homogeneously distributed within the psoriasis lesion skin, the appearance of which indicates that the elongated loops are perpendicular to the surface of the skin. The regions of interest scanned were $\sim 2\ \text{mm} \times 2\ \text{mm}$. The scale bar is 0.5 mm.

Fig. 7. Histogram distribution for the blood vessel density (*BVD*) values obtained from the normal skin and psoriatic skin. Blue bars are for the normal skin and the red bars for psoriatic lesion skin. The bell-curves are obtained by fitting the *BVD* values in each group to the normal distribution function.

Fig. 8.
Error bar graph of *BVD* values of normal skin and lesion skin. (n=50 per group, $*P < 0.001$ at $\alpha=0.01$)