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In vivo tissue injury mapping using OCT based methods

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Abstract

An injury causes changes in the optical attenuation coefficient of light beam travelling inside a tissue. We report a method called tissue injury mapping (TIM), which utilizes a non-invasive *in vivo* optical coherence tomography approach to generate optical attenuation coefficient and microvascular map of the injured tissue. Using TIM, the infarct region development in mouse cerebral cortex during stroke is visualized. Moreover, we demonstrate the changes in human facial skin structure and microvasculature during an acne lesion development from initiation to scarring. The results indicate that TIM may be used to aid in the characterization and the treatment of various diseases by enabling a high resolution detection of tissue structural and microvascular changes.

1. INTRODUCTION

In vivo methods for non-invasive characterization of tissue properties have started to draw attention in the community for the accurate determination of the extent and the spread of disease within tissue. Tissue characterization techniques often rely on the fact that the disease alters physical characteristics of the tissue and this alteration can cause observable changes in the received signal (either optical or acoustic), primarily through absorption and scattering. Changes in the signal attenuation decay within tissue, measured as an attenuation coefficient, can be used to differentiate various tissue types with pathological conditions. The first use of this idea goes back to 1980s where an acoustic attenuation coefficient was used in ultrasonic tissue characterization [1] for a wide range of applications such as diseased tissue assessment on liver [2], breast [3] and eye [4].

Optical coherence tomography (OCT) is a real-time, non-invasive 3D imaging technique that provides major advantages over ultrasound imaging by producing millimeter-scale morphological views of tissue microstructures *in vivo* with higher resolution ($\sim 5 \mu\text{m}$), analogous to histology [5]. Since the introduction of OCT in the early 1990s [6], measuring optical attenuation coefficient (OAC) using OCT signals became a popular tool for *in vivo*

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characterization of various tissue injury or disease types, i.e. atherosclerosis [7], burn scar [8], glaucoma [9], and ischemic brain [10].

Moreover, by analyzing OCT signals, volumetric blood perfusion map of tissue down to capillary level can be extracted from perfused tissue *in vivo* using optical microangiography (OMAG) [11, 12]. During the last few years, OMAG technique has been intensively used to study the microvasculature of a variety of biological tissues *in vivo*. For example, OMAG has been recently used to investigate the vascular abnormalities in human facial skin with acne vulgaris [13]. It has also been used to study mouse cerebral microvasculature [14, 15], and to image capillary morphology inside a healthy and an inflamed human skin *in vivo* (16, 17).

Tissue injury affects both microvasculature and cellular structure [8]. OAC reconstruction alone can only provide the information about structural changes in tissue and cannot connect it with the microvascular remodeling during the injury and the recovery periods. Here, we combine the OAC reconstruction method recently developed by Vermeer et.al [9] with OMAG for more detailed tissue injury mapping (TIM). OMAG provides an important additional information about the extent of injury by generating a high resolution map of microvasculature. We also propose a useful and yet simple algorithm called sorted average intensity projection (sAIP) for en face mapping of the reconstructed OACs belonging to different tissue types. The results of TIM on a mouse model during middle cerebral artery occlusion and on human facial skin with an acne vulgaris lesion are presented in section 3.1 and 3.2, respectively. The results demonstrate that such TIM results provide improved tissue contrast over standard en face OCT images. We believe that the acquired high-quality, detailed TIM images of injured human skin and mouse brain would deliver an alternative and/or complimentary tool to facilitate treatment and diagnosis of several diseases.

2. METHODS

1. Attenuation Coefficient Mapping

To calculate an OAC in an OCT signal, typically simple single backscattering of light is assumed using the following equation:

$$I(x) = I_0 \rho e^{-2\mu x} \quad (1)$$

where I represents the value of the detected intensity, I_0 is the intensity of incident light, ρ is the backscattering coefficient, μ is the OAC, x is the depth. Factor of 2 comes from the fact that light travels round trip within tissue. The common way to calculate an OAC is by extracting the decay constant upon fitting an exponential curve to the backscattered signal. The major drawback of this approach is that it is difficult, if not impossible, to accurately separate different layers without pre-segmenting and pre-averaging a large amount of data. Moreover, the vasculature inside the tissue generates a shadowing effect due to the strong forward scattering at red blood cells, causing artificially high attenuation of the OCT signal that is not representative of the surrounding nonvascular component of the tissue [8].

Recently, Vermeer et.al [9] developed a simple method to estimate the attenuation coefficients locally where every pixel in the OCT data set is converted into a corresponding OAC pixel using the following relationship:

$$\mu[i] \approx \frac{I[i]}{2\Delta \sum_{i+1}^{\infty} I[i]} \quad (2)$$

Here $I[i]$ is the OCT signal at a certain pixel, Δ is the pixel size and $\mu[i]$ is the OAC at that pixel. It produces accurate results for both homogeneous and heterogeneous tissue and does not require pre-segmenting or pre-averaging of data. Moreover it does not suffer significantly from the shadows of the blood vessels at the deeper layers, since it calculates the OAC separately at each pixel in contrast to fitting a curve along the depth in the region of interest.

We combine this approach with en face sAIP method. To do so, we first select the tissue volume from the 3D OAC data and then sort the values of OACs in the each A-line in an ascending order. Then we use one of the following equations to calculate the average OAC at a specific en face location, defined as $\mu_{average}[y]$:

$$\mu_{average_1}[y] = \frac{\sum_{i=(N/2)-(M/2)}^{(N/2)+(M/2)} \mu_{sorted}[i]}{M} \quad (3)$$

$$\mu_{average_2}[y] = \frac{\sum_{i=N-M-D}^{N-D} \mu_{sorted}[i]}{M} \quad (4)$$

Here, $\mu_{sorted}[i]$ is the value of the i^{th} OAC and N is the total pixel number in the selected portion of the each A-line. M and D are adjustable parameters that determine the number of pixels to be averaged and the number of pixels to skip, respectively. Averaging several OACs after sorting removes the possible fluctuations in individual OACs and produces a smooth en face map as in Fig. 1c. M parameter should be picked based on the size of the region of interest. Averaging excessive number of pixels would make detection of small changes difficult. Moreover, D parameter can be used to remove the unwanted portion of the data, such as surface reflection. Both parameters depend on the system sensitivity, the optics and the tissue.

2. Optical Microangiography

To visualize the volumetric microvasculature up to capillary level, an OCT based OMAG technique is utilized [18]. For the mouse cerebral cortex imaging, the data is acquired with 180 frames per second (fps) where every B-frame is made of 400 A-lines covering a total distance of approximately 2 mm. The slow axis (C-scan), consisting of 3200 B-frames, covers the same distance by repeatedly scanning eight times at each location, result in the construction of 3D image in about 18 seconds. A Doppler OMAG [19] measurement of the same area is conducted following OMAG, which shows the axial velocity map of cerebral

blood flow with the range of ± 6.1 mm/s. It took about 100 seconds to acquire the 3D image. Details of these protocols can be found in [14].

For the human facial skin imaging, fast B-scans in the X direction consists 256 A-lines, and slow C-scans in the Y direction are made of 2048 B-frames where each scan is repeated eight times at each location. This takes approximately 20 seconds covering $3\text{mm} \times 3\text{mm}$ area when the imaging rate is set at 100 fps. Details of this protocol can be found in [13]. These imaging protocols are repeated multiple times at multiple connected locations to create a final mosaic image to effectively increase the field of view.

3. RESULTS

The animal procedures performed in this study are approved by the Institute of Animal Care and Use Committee (IACUC) of the University of Washington. The high resolution images of the cortex were taken through the open skull cranial window [14], using the spectral domain OCT system [20] with a superluminescent diode (Thorlabs Inc.) as the light source, which has a central wavelength of 1340 nm with a bandwidth of 110 nm, providing a ~ 7 μm axial resolution in the air. In the sample arm, 10X scan lens (Thorlabs Inc.) was used to achieve ~ 7 μm lateral resolution. The linescan camera (Goodrich Inc.) used in the spectrometer had 92 kHz line rate. The area under the window (parietal cortex) corresponded to the supplying territory of distal branches of both the middle cerebral artery (MCA) and anterior cerebral artery (ACA), and was subjected to imaging during baseline, MCA occlusion [21], and reperfusion periods.

The en face OAC mapping using sAIP provides significant advantages over the en face AIP of OCT structural data by providing more accurate tissue optical property information with significantly less blood vessel shadowing artifacts. Fig. 1 compares the AIP of OCT structural and OAC 3D data sets during MCA occlusion in mouse. Fig. 1a shows the en face maximum intensity projection (MIP) of microvasculature in the pial layer. As can be seen in Fig. 1a, most of the capillaries disappear from the MCA side during occlusion, which lead to a potential infarct development. The progression of this region causes scattering changes in the tissue, and can be distinguished from the healthy region (this will be investigated more in the next section). The en face sAIP of the OAC data in Fig. 1c shows a clear difference between MCA and ACA sides after MCA occlusion. On the other hand, the en face AIP of the structural data comes with the blood vessel shadowing artifacts and thus provides a non-uniform map of tissue characteristics. This can also be observed from the cross-sectional images in Fig. 1e–f.

1. Tissue injury mapping during stroke on mouse cerebral cortex

During the MCA occlusion, the lack of blood supply from the MCA side leads to an ischemic state. Energy deficits in an ischemic tissue result in cellular morphology and light scattering changes after anoxic depolarization [22]. Using TIM, we showed the tissue microvasculature and scattering changes from healthy to ischemic and infarct tissue states.

The cerebral blood flow images were obtained through merging 9 OMAG images and 4 Doppler OMAG images as mosaics in Fig. 2. The bidirectional en face MIP images in Fig.

2(a–c) show the diving arterioles and the rising venules as green and red spots, respectively, where the RBC axial flow velocity information is coded with a color bar in a range of ± 6.1 mm/s. Moreover, the OMAG images in the pial region of the mouse cerebral cortex is given in Fig. 2(d–f), where the en face MIP of capillaries up to 100 μm depth is demonstrated, which was arranged to stay in the depth of focus of the lens. Lastly, the en face sAIP of OAC images are shown in Fig. 2(h–i). Accordingly, during the occlusion, the average OAC in the ischemic region (MCA side) starts to increase compared to the basal condition, potentially revealing the penumbra (region destined for infarction). After 60 min of occlusion, although some of the blood flow is restored during the reperfusion, the average OAC in the MCA side keeps increasing sharply, representing the infarct region. Here, TIM proves to be useful by providing complimentary information about both the microvascular and structural responses to stroke. It is also important to note that the cyanoacrylate glue used in the cranial window preparation [14] might affect the results at the edges.

2. Tissue injury mapping on human skin

To visualize the transition from acne lesion initiation to scarring stages, longitudinal changes in a selected acne lesion on human facial skin is monitored using a swept-source OCT system (Thorlabs Inc.) described in [13]. Briefly in this system, the source is able to sweep the lasing wavelength across a broad spectral range near 1310 nm at a fixed repetition rate of 100 kHz with 15 μm axial resolution in tissue. A 5X objective lens (Thorlabs Inc.) is used in the sample arm to achieve 22 μm lateral resolution.

Fig. 3 demonstrates the tissue scattering and microvascular changes in the acne lesion during initiation, development and scarring stages. The results from these three stages are grouped, in which, the photographs of the acne lesion (top), the en face MIP images of volumetric microvasculature (middle), and the en face sAIP of OAC images (bottom) are given.

The en face MIP of volumetric microvasculature image of acne lesion in Fig. 3d shows that most of the blood vessels in the lesion area are damaged during the acne initiation stage. In Fig. 3g, the en face sAIP of OAC data promotes better visualization and localization of the borders of the tissue injury, caused by the alterations in optical properties of the skin induced by collagen or other tissue damage or by inflammation during acne lesion initiation. Here, region with a lighter color in the middle (pointed out with yellow dashed line) represents the area with the coagulation and inflammatory cells. On the other hand, surrounding darker region (pointed out with blue dashed line) represents the disturbed dermal layer, which is caused by the edema that is mostly consisting of inflammatory cells and liquid waste. Since there is less light scattering in this region compared to middle region, it looks darker on the en face sAIP of OAC data.

In the development stage of the acne lesion, the en face MIP of volumetric microvasculature image in Fig. 3e shows that the vessel density in the lesion increases significantly. Moreover, the en face sAIP of OAC data (Fig. 3h) indicates that the remodeling activity in the middle of the acne lesion continues, leading to a higher average OAC, and outer region still lacks a fully repaired dermal layer which leads to a lower average OAC (appears darker on the image).

Lastly, at the day 50, Fig. 3c shows that the acne lesion turns into a scar. This time, the en face MIP of volumetric microvasculature image (Fig. 3f) shows that the vessel density in the original lesion area is decreased to a level similar to the surrounding healthy area. On the other hand, the en face sAIP of OAC data (Fig. 3i) of the lesion appears more uniform compared to the previous stages.

3. Contrast comparison between OAC mapping methods

For a relatively homogeneous tissue, e.g. cortex, we average the middle pixels in the sorted data using Eq. (3) to remove the possible inaccurate part due to noise and multiple scattering effects. On the other hand, for a heterogeneous tissue, e.g. skin, we average the pixels close to the highest intensity using Eq. (4) to capture the dermal layer we are interested in. We compared the contrast of OAC maps generated by different projection methods, sAIP, AIP, and maximum intensity projection (MIP), in Fig. 4. Here, contrast ratio, C , is defined in Eq. 5:

$$C = \frac{I_{injured} - I_{healthy}}{I_{healthy}} \quad (5)$$

where $I_{injured}$ and $I_{healthy}$ are mean values of pixel intensities in regions (3×3 pixels) collected from 25 different parts of the injured and healthy areas in the image, respectively.

Results in Fig. 4 shows that sAIP provides a better contrast to AIP method and comparable contrast to MIP method for a relatively homogeneous tissue such as cortex using Eq. 3. On the other hand, sAIP method using Eq. 4 is clearly superior to both alternative methods for a relatively heterogeneous tissue such as human skin. Scattering and absorption are typically higher in dermis compared to epidermis in human skin. When we sort the data in an ascending order, the first few pixels (highest intensity pixels) typically belong to the surface reflection and the rest are expected to belong to dermis. In Eq. 4, parameter D is used to skip the surface reflection pixels from the averaging. MIP projection method picks the surface reflection pixels over dermis ones, and AIP method mixes the dermis and epidermis signals which reduce the contrast. Moreover, average C values are calculated below 0.02 among the same tissue types, which lead to visually uniform images. Using sAIP method, without requiring pre-segmentation and complicated image processing algorithms, we are able to provide high contrast map of injured and healthy tissue regions for en face TIM applications.

4. DISCUSSION AND CONCLUSION

Stroke is a major disease that has been heavily researched on. The severity and the duration of ischemia are the two major biomarkers for the assessment of ischemic damage during stroke. The impairment of physiological properties of neurons caused by an ischemia can be reversible depending on the severity of the ischemia and the time duration without proper reperfusion. The tissue surrounding the infarct core with a salvageable status is called penumbra. The penumbra dies as the infarct core expands over time.

Magnetic resonance imaging [23] is the most popular clinical indicator for the tissue at risk during stroke and remains the best performing diagnostic tool for clinical research and therapy on humans [24]. However, it does not provide high resolution imaging capability to conduct stroke studies on rodent brain. Experimental stroke research is in need of new non-invasive microscopic *in vivo* imaging techniques to investigate brain recovery mechanisms. TIM is a promising tool to provide high resolution *in vivo* imaging of rodent brain during stroke. The results of TIM imaging on mouse cortex during MCA occlusion (Fig. 2) indicate that the OAC and OMAG may be successfully combined as an indicator to show the status of brain tissue, providing useful information on the critical time zone for treatment to rescue the part of cortex exposed to severe hypoxia. Detailed studies can be conducted using TIM imaging to discover new therapeutic methods for stroke.

In addition to stroke research, TIM can also be used in the investigation of human skin diseases like acne vulgaris. Acne vulgaris is a distressing skin disease, prevalent in the majority of the younger population, which can affect the quality of life for those affected. The *in vivo* TIM imaging results clearly demonstrate the tissue property and microvascular changes during acne lesion development stages in a great detail. As shown in Fig. 3, breakage of dermis naturally leads to hypertrophic scarring observed with dense microvasculature and increased optical scattering. After the healing of dermis, the map of tissue optical properties become more uniform and dense microvascular presence returns to normal.

Moreover, based on the results presented, it is reasonable to hypothesize that the TIM imaging can be used to utilize OAC and vascular density as biomarkers in the monitoring, therapeutic treatment and management of other prevalent skin diseases in general, e.g. port wine stain (PWS), psoriasis, skin burn, and skin cancer. For instance, replacing a standard visual inspection of the skin burn, the scar vascular density and scattering property map can be potential indicators to assess the scar progression, and might help improve the accuracy of diagnosis and treatment of pathological scarring. Furthermore, skin cancer can be better visualized and understood for treatment and research purposes without using invasive techniques.

The OAC reconstruction method is based on two major assumptions: the most of the light is attenuated within the recorded imaging depth range, and only the fixed ratio of the probing light backscatters from the attenuated light, i.e., backscattering coefficient is constant. Due to the limited penetration depth of OCT signal in tissue, the first assumption holds. On the other hand, second assumption is not valid for heterogeneous tissue types like human skin, and this might lead to inaccurate estimate of OAC using this method. However, it still effectively delineates different tissue types [9]. It is important to note that the dashed lines are provided in the figures to point out the observable changes and further studies are required to correlate local contrast changes with histology results.

In summary, *in vivo* non-invasive TIM imaging can clearly delineate the structural and microvascular changes in tissue during various injury conditions. The results demonstrated significant advantages of utilizing OCT based TIM to assess tissue structural and microvascular changes during stroke on mouse cerebral cortex and acne lesion development

on human skin. Further well-designed studies are required to systematically investigate and establish the benefits of this technique for specific applications. Nevertheless, earlier results are promising that TIM can become a major tool to help clarify the complex mechanisms of tissue injury and contribute to the clinical management and development of new treatment alternatives for various diseases.

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Fig. 1.

Comparison between OMAG, OCT structural and OAC images during MCA occlusion. (a) En face maximum intensity projection of OMAG image. (b) En face AIP of OCT structural image. (c) En face sAIP of OAC image. (d–f) Cross sectional views of OMAG, OCT structural image and OAC image, respectively, at a location delineated with blue dashed line. Yellow dashed line point out the border between healthy and infarct region. Scale bar represents 0.2 mm.

Fig. 2.

TIM of 3D data set on mouse cerebral cortex through cranial window during basal, 60 min MCA occlusion and reperfusion conditions. (a–c) En face MIP of axial velocity distribution at 0 – 500 μ m depth. (d–f) En face MIP of microcirculation network at 0 – 100 μ m depth. (g–i) En face sAIP of OAC image. Dashed red lines point out areas with the changes in the tissue scattering properties. Scale bar represents 0.4 mm.

Fig. 3.

TIM of 3D data set during acne lesion initiation, development and scarring on human facial skin. (a–c) Photographs of the imaged acne lesion on day 1 (a), day 15 (b), and day 50 (c). (d–f) En face MIP of microcirculation network for corresponding days at 0 – 1mm depth. (d–f) En face sAIP of OAC data at 200 μm – 1mm depth. Scale bar represents 1 mm.

Fig. 4. Contrast comparison using Eq. 5 between en face sorted average intensity projection (sAIP), average intensity projection (AIP) and maximum intensity projection (MIP) of OAC images from mouse cortex and human skin with acne lesion, acquired using OCT and generated through the OAC analysis. (a–c) En face OAC images of mouse cortex during MCA occlusion generated using (a) sAIP with Eq. 3, (b) AIP, and (c) MIP. (d–f) En face OAC images of human skin with acne generated using (d) sAIP with Eq. 4, (e) AIP, and (f) MIP. (g–h) Contrast ratio comparison between projection methods using (g) cortex data, (h) human skin data. Dashed lines point out the borders between injured and healthy tissues. * $P < 10^{-5}$ significantly different data sets (paired t-test). Scale bar represents 0.2 mm.