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Retinal blood flow measurement with ultrahigh-speed swept-source / Fourier domain optical coherence tomography

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ABSTRACT

Doppler OCT is a functional extension of OCT that provides information on flow in biological tissues. We present a novel approach for total retinal blood flow assessment using ultrahigh speed Doppler OCT. A swept source / Fourier domain OCT system at 1050 nm was used for 3D imaging of the human retina. The high axial scan rate of 200 kHz allowed measuring the high flow velocities in the central retinal vessels. By analyzing en-face images extracted from 3D Doppler data sets, absolute flow for single vessels as well as total retinal blood flow can be measured using a simple and robust protocol.

Keywords: Optical coherence tomography, blood flow, retinal imaging

1. INTRODUCTION

Abnormalities in retinal blood flow occur in several ocular diseases such as glaucoma, diabetic retinopathy and age-related macular degeneration.\textsuperscript{1-3} Accurate knowledge of ocular perfusion is important not only for treatment but also for understanding the pathophysiology of these diseases which can lead to blindness. Hence, there is great demand for methods for assessment of ocular blood flow in vivo. In the last decades, different techniques have been developed to assess perfusion in the human eye.\textsuperscript{4}

Angiographic methods allow for visualization of vascular structures by imaging an injected fluorescent dye. The Doppler effect has been exploited for techniques such as ultrasound-based color Doppler imaging, laser Doppler velocimetry or Doppler optical coherence tomography (OCT). Color Doppler imaging (CDI) combines B-mode images with velocity information obtained from the Doppler shift of the erythrocytes moving in the retrobulbar vessels.\textsuperscript{5} CDI is able to access information on pulsatile blood flow; however, total blood flow cannot be determined since the vessel diameters cannot be quantified with this technique. Laser speckle techniques, which estimate flow velocity from the rate of variation of the speckle pattern, suffer from the same drawback. Laser Doppler velocimetry (LDV) is an approach to measure blood velocity in retinal arterioles and venules using the Doppler shift of light. From an additional measurement of the retinal vessel diameter, the total blood flow in a single vessel can be calculated.\textsuperscript{6,7} The Canon Laser Doppler blood flowmeter is a commercially available instrument that combines LDV with a retinal vessel diameter assessment system, thus making it the only device on the market that can measure retinal volumetric blood flow – one of the key parameters for understanding retinal physiology – in absolute units.\textsuperscript{7,8}

OCT is an emerging technique for non-contact imaging of transparent and translucent tissue with micrometer scale resolution.\textsuperscript{9} In ophthalmology, due to its ability to perform depth-resolved cross-sectional imaging of retinal structures, OCT has evolved into an indispensable tool for diagnosis of eye disease and for monitoring during therapy.\textsuperscript{10} Recent advances in terms of sensitivity and imaging speed using Fourier domain OCT techniques have enabled the acquisition of three dimensional (3D) data sets comprising several tens or even hundreds of thousands of axial scans within a few
Fourier domain OCT can be performed either using spectrometer based detection (spectral / Fourier domain OCT) or using a swept laser source (swept source / Fourier domain OCT).\textsuperscript{17-19}

Doppler OCT (or optical Doppler tomography, ODT) is a functional extension of OCT that enables the detection flow in biological tissues.\textsuperscript{20, 21} Doppler OCT combines the principles of LDV and OCT by detecting Doppler shifts generated by moving scatterers as a function of depth. In contrast to most other techniques used for blood flow measurements, Doppler OCT provides both structural and functional information. Using Fourier domain Doppler OCT, retinal and choroidal vasculature has been visualized in 3D.\textsuperscript{22-26}

Several approaches have been used to assess total blood flow in retinal vessels. Since Doppler OCT measures only the velocity component parallel to the probe beam, usually the Doppler angle, \textit{i.e.} the angle between flow direction and probe beam, must be determined from the retinal structure in order to calculate absolute flow velocities.\textsuperscript{27-30} Using the absolute flow velocity and measuring the vessel cross-section area, total flow values can be calculated. Another approach is to detect Doppler shifts from different directions by illuminating the retina with two beams impinging at different angles, similar to bidirectional LDV.\textsuperscript{31} This approach does not require knowledge of the vessel angle, but has the additional complexity of requiring two beams.

In this contribution, a new approach for measuring total retinal blood flow is presented which is based on a technique for cerebral blood flow measurement recently published by Srinivasan \textit{et al.}\textsuperscript{32} This technique does not require measurement of the Doppler angle, but instead measures the flow at a Doppler angle of 0°, \textit{i.e.} in a plane perpendicular to the probe beam. An ultrahigh speed swept source OCT instrument operating at 200 kHz was used for imaging the optic disk in healthy eyes in vivo.\textsuperscript{33} This system is especially suited for Doppler OCT because (1) the high speed enables dense sampling of 3D data sets as well as the detection of high flow velocities,\textsuperscript{25, 34} (2) the 1-μm wavelength range has been demonstrated to provide higher penetration into the retina and optic nerve, thus enabling the measurement of papillary retinal vessels,\textsuperscript{35-38} and (3) swept source detection has been shown to be more robust to fringe washout when detecting high flow velocities.\textsuperscript{39, 40}

## 2. METHODOLOGY

### 2.1 OCT system

A sketch of the OCT system is shown in Figure 1. The system is based on a recently developed ultrahigh speed swept source / Fourier domain OCT instrument.\textsuperscript{33} A commercially available swept laser was used as a light source (Axsun Technologies, Inc.). The swept output spectrum of the laser was centered at 1050 nm and had a FWHM bandwidth of 100 nm. The fundamental sweep rate of the laser was 100 kHz. Since the laser was emitting light during the forward sweep only, its duty cycle was ~51 %. A long length of single mode fiber was used to delay part of the original sweep by ~5 μs and hence to double the sweep rate to 200 kHz. Polarization controllers and a linear polarizer were used to match the output polarizations of sweep and delayed copy at the end of the buffering stage. In order to compensate for the power losses in the buffering stage and the polarizer, a broadband semiconductor optical amplifier (SOA, Inphenix, Inc.) was used to boost the power at the input of the OCT interferometer. Excessive power was attenuated by inserting an additional fiber coupler after the SOA.

The OCT system featured a transmissive reference arm with glass plates and a water cell for dispersion compensation. In the sample arm, light was split with a 99/1 coupler. The majority, 99 %, of the light was directed a slit lamp interface incorporating the galvanometers and scanning optics to steer the OCT beam across the retina under investigation. A small fraction, 1 %, of the light was used to provide a stable phase reference signal from a glass plate located at a depth of ~2 mm in the OCT image. Light returning from the sample and reference arms interfered at a 50/50 coupler and was detected by a balanced receiver (Thorlabs, Inc.). The interference fringes were recorded by a high speed digitizer (Innovative Integration, Inc.) with a rate of 400 MHz and 14 bit resolution. The system sensitivity was measured to be 95 dB. Standard OCT processing was performed and included remapping of the spectral interferograms to linear sampling in k-space, zero-padding and Fourier transforming to generate the complex depth scans.
2.2 Assessment of Doppler flow velocities and compensation for phase artifacts

Depth resolved axial flow velocities can be calculated from the phase shift $\Delta \Phi_{Doppler}(z)$ between neighboring axial scans as $v(z) = \Delta \Phi_{Doppler}(z) / (k T)$, where $k$ is the wavenumber and $T$ is the time elapsing between the two axial scans.\textsuperscript{20, 21} For this study, Doppler flow velocities were calculated between every other axial scan (i.e., between sweeps only) and between every scan (i.e., between axial scans from sweeps and copies) in cross-sectional images. The respective maximum velocities that correspond to phase shifts of $\pm \pi$ are $\pm 25$ mm/s and $\pm 50$ mm/s for 100 kHz and 200 kHz, respectively.

Different phase artifacts obscured the actual flow velocity profiles and needed to be compensated for (Figure 2). In addition to the Doppler shifts caused by moving scatterers in the retinal blood vessels, axial eye motion and vibrations in the OCT system resulted in bulk motion artifacts offsetting the Doppler shifts of the entire retinal signal. Since the stationary retinal structure is also affected by this bulk motion artifact, the Doppler shift offset at the retinal surface was detected and subtracted from the entire axial scan.\textsuperscript{23} Another contribution to phase shift artifacts is caused by a fluctuation of the data acquisition line trigger generated by the laser light source at the beginning of every sweep. Since any shift of the sampled spectral interferograms in time results in a spectral shift $\delta k$, using the Fourier shift theorem, the resulting phase difference between subsequent axial scans is given by $\Delta \Phi_{rig} = 2\pi \delta k z$. By implementing a phase reference arm with reference reflections far away from the zero delay, this phase ramp was sampled at two different depth positions in order to estimate the slope of the ramp as shown in Figure 2(B).\textsuperscript{41, 42}

2.3 Total retinal blood flow measurement using en-face images

Total blood flow computation was performed using an algorithm based on a recent publication by Srinivasan et al.\textsuperscript{32} Unlike previous methods, knowledge of the Doppler angle, i.e., the angle between vessel and probe beam, is not required. Absolute flow values can be computed from 3D Doppler OCT data by integrating the flow components in a plane bisecting vessels perpendicular to the probe beam, i.e., in an en-face plane.\textsuperscript{32}
where $v_z(x,y)$ denotes the axial flow velocity in the en-face plane.

In most areas of the retina, the blood vessels are almost parallel to the retinal surface. Therefore, if blood flow is to be determined using this approach, the central retinal vessels in the optic disk must be imaged. In the optic disk, the vessels are almost parallel to the OCT beam, and all vessels can be intersected by a volumetric data cube. However, the flow velocity components in the direction of the OCT beam are high (up to ~50 mm/s), therefore high axial scan rate and deep penetration into the optic nerve are required.

3. RESULTS AND DISCUSSION

3.1 Three-dimensional imaging of retinal vasculature

The ultrahigh speed swept source / Fourier domain OCT instrument was used to record volumetric data sets consisting of 250 B-scans consisting of 2000 axial scans each in 2.5 s. Retinal imaging was performed with an incident average power of 1.9 mW, consistent with the exposure limits drawn by the American National Standards Institute (ANSI) standards. The study protocol was approved by the institutional review board of the Massachusetts Institute of Technology. Written informed consent was obtained prior to the study.

Figure 3 shows example results from volumetric imaging of the optic disk region in the retina of a healthy subject. The treelike branching of retinal arteries and veins can nicely be appreciated in the 3D renderings of Doppler images at 100 kHz before (top) and after phase correction (bottom).
kHz and 200 kHz computed from the same spectral data (Figure 3(A) and (B)). Blood flow can be visualized even in the central retinal arteries deep in the papilla. Figure 3(C) and (D) show examples of Doppler B-scan images at 100 kHz and 200 kHz. Note the different velocity ranges for the two images. At 100 kHz axial scan rates, there is still phase wrapping in the central retinal vessels where the flow velocities are high. However, no phase wrapping artifacts were observed at 200 kHz repetition rates.

Figure 3. 3D Doppler imaging of the vasculature in the optic disk region of the human retina using ultrahigh speed swept-source / Fourier domain OCT. 3D renderings of volumetric data sets at 100 kHz (A) and 200 kHz (B) show the tree-dimensional structure of the retinal arteries and veins branching in the optic disk. Cross sectional Doppler OCT images show blood flow in two arteries and veins close to the papilla. The color maps encode velocity ranges of ±25 mm/s and ±50 mm/s for 100 kHz (C) and 200 kHz (D) Doppler images, respectively.

Figure 4 shows a comparison of the ability of ultrahigh-speed OCT to generate en-face images of both the retinal structure and functional information about blood flow in the optic disk with standard ophthalmic imaging methods. Color fundus photography and OCT fundus projection images visualize comparable details of the vascular morphology in the papilla (Figure 4(A) and (B)). In Figure 4(C), an early phase fluorescein angiography image of the same retinal region enables to distinguish features of arterial and venous vasculature. Blood flowing in central retinal arteries and veins can also be observed in the ultrahigh speed Doppler OCT en-face projection image of Figure 4(D). Blood flowing in and against the direction of the OCT beam is displayed in red and blue color, respectively. Note that, in contrast to fluorescein angiography, OCT enables non-invasive and contact-free imaging and provides depth-resolved assessment of retinal blood flow.
Figure 4. Fundus images of the optic disk in a healthy eye. (A) Color fundus photography showing the retinal vasculature. Note that venous vessels carrying deoxygenated blood appear in slightly darker color. (B) Fundus projection image computed from a 3D OCT data set acquired with the ultrahigh speed swept source / Fourier domain OCT instrument. (C) Fluorescein angiography image taken immediately (14.7 s) after injection of the dye allows for clear differentiation between arteries and veins. (D) Ultrahigh speed Doppler OCT image shows blood flowing in central retinal arteries and veins. Blood flowing in positive direction (towards the pupil) is displayed in red, negative flow appears in blue color.

3.2 Quantitative assessment of total retinal blood flow

Total flow was measured in the optic disk by integrating over the vessels in en-face images using the method for flow measurement described in section 2.3. Flow was calculated for individual vessels in different en-face images over a depth of 120 μm (Figure 5). The depth range over which flow calculations were performed is indicated in the Doppler OCT cross-sectional image in Figure 5(A). For all vessels investigated, only small variations between measurements at different depths were observed. The mean flow values were 6.8 μL/min, 15.5 μL/min, and 26.6 μL/min in the retinal arteries A1, A2, and A3 in the en-face image of Figure 5(B). The total arterial flow of 50.7 μL/min was computed as the sum of A1 – A3. The average total arterial flow computed in a larger region of interest around the optic disk was 49.0 μL/min with a coefficient of variation (standard deviation / mean) of 5.2%.
Figure 5. Measuring total blood flow in different depths of the optic disk. (A) Doppler OCT B-scan image. The depth range in which en-face flow measurements were performed is indicated. (B) En-face Doppler OCT image. Central retinal arteries labeled A1 – A3 and veins (V) can be observed. (C) Blood flow measured at different depths in A1 – A3 and total arterial blood flow computed by summing the flow values for the single retinal arteries (A1+A2+A3) as well as by integrating blood flow towards the OCT beam in a large area covering all vessels.

4. CONCLUSION

Structural imaging of retinal vasculature as well as quantitative assessment of retinal blood flow was demonstrated using a novel ultrahigh-speed swept-source / Fourier domain OCT instrument. This approach has several advantages: Imaging at 1050-nm wavelengths provides enhanced penetration into deep ocular structures. The rapid axial scan rate enables detection of high flow velocities up to ±50 mm/s. Swept-source OCT is less sensitive to phase washout compared to spectrometer-based Fourier domain systems. Hence, swept source OCT promises to be a powerful tool for in vivo assessment of blood flow in healthy and diseased eyes.

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