Optics Letters

Imaging pulse wave propagation in human retinal vessels using full-field swept-source optical coherence tomography

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Received 10 July 2015; revised 21 September 2015; accepted 22 September 2015; posted 23 September 2015 (Doc. ID 245484); published 14 October 2015

We demonstrate a new noninvasive method to assess biomechanical properties of the retinal vascular system. Phase-sensitive full-field swept-source optical coherence tomography (PhS-FF-SS-OCT) is used to investigate retinal vascular dynamics at unprecedented temporal resolution. The motion of retinal tissue that is induced by expansion of the vessels therein is measured with an accuracy of about 10 nm. The pulse shapes of arterial and venous pulsations, their temporal delays, as well as the frequency-dependent pulse propagation through the capillary bed, are determined. For the first time, imaging speed and motion sensitivity are sufficient for a direct measurement of pulse waves propagating with more than 600 mm/s in retinal vessels of a healthy young subject.

OCIS codes: (170.4470) Ophthalmology; (110.4500) Optical coherence tomography; (170.2655) Functional monitoring and imaging; (170.6920) Time-resolved imaging.

http://dx.doi.org/10.1364/OL.40.004771

In the last years, the retinal vascular system has increasingly attracted attention, not only in ophthalmology, but also in cardiology and internal medicine. This is due to the fact that cardiovascular pathologies could possibly be diagnosed in early stages by a noninvasive evaluation of biomechanical properties of the retinal vascular system [1]. However, fluorescein and indocyanine green angiography merely provide structural information about the retinal vessel network. Optical coherence tomography (OCT)-based angiography, which employs motion contrast imaging, additionally contains functional information on blood flow velocity, but so far it does not provide any quantification of biomechanical properties of the retinal vascular system or the surrounding tissue.

One important biomechanical parameter is the elasticity of retinal vessels, which can be determined by measuring the pulse wave velocity (PWV) in these retinal vessels [2]. So far, two different methods were employed. The first and most common one is the retinal vessel analyzer (RVA) [1], which records 25 fundus images per second to determine temporal changes of vessel diameters using image processing algorithms. The second method is based on the evaluation of video-rate fluorescein angiographies [3]. Both methods suffer from a signal-to-noise ratio (SNR) that is too low for a direct evaluation of the raw data and, thus, require sophisticated signal processing, including narrow band-pass filtering at the cardiac frequency. Hence, the evaluation of vascular dynamics is limited to the heart beat frequency, and neither the pulse shape nor any frequency-dependent quantity can be determined. If the PWV in human retinal arteries is in the order of 1 m/s, as is suggested from previous animal studies [4–6] and theoretical models such as the Moens–Korteweg equation [2], a frame rate of at least 100 Hz is required to sample the propagation of the pulse wave along a retinal vessel. However, measurements so far were limited by a frame rate of just 25 Hz. Furthermore, the published results for pulse wave velocities in human retina of healthy young subjects varied by two orders of magnitude between 400 μm/s measured by the RVA [1] and 20 mm/s measured by the RVA and fluorescein angiographies [3,7].

High-speed phase-sensitive spectral-domain OCT has been shown to be a suitable tool to quantify the pulsatile motion of the optic nerve head at 500 frames per second [8]. Moreover, it is sensitive to motion of just 0.3 nm, thus providing a sufficiently high SNR for the measurement of axial motion on a micrometer scale. The spatial resolution, however, is limited to just one lateral scan line, half of which is needed to compensate for global motion. To investigate the propagation of pulse waves in retinal vessels, however, a 2D field of view has to be recorded.

Here we demonstrate PhS-FF-SS-OCT as a new method to investigate retinal vascular dynamics. It provides a temporal

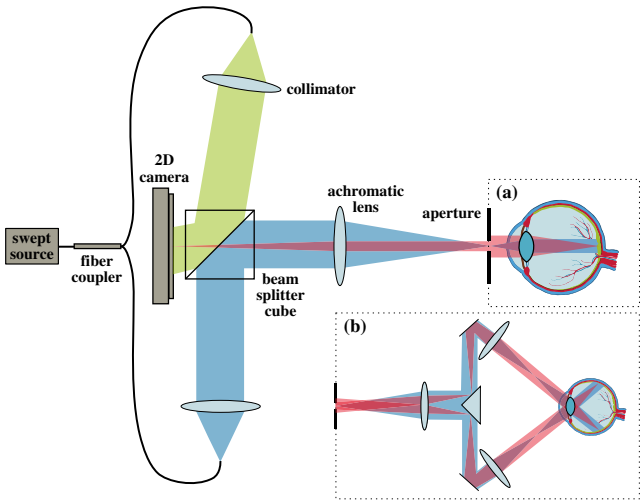

Fig. 1. Setup for FF-SS-OCT. The light of a wavelength tuned laser source is split into sample illumination (blue) and reference wave (green). The latter is superimposed with backscattered sample light (red) on the 2D camera sensor. To split the field of view, the components in frame (a) were replaced by those in frame (b).

resolution of 0.5 ms and is capable of measuring axial expansion of just some nanometers. The arterial and venous pulse shapes and the time delay between their pulsations, as well as the PWV, were measured in the retina of a healthy young subject.

The full-field swept-source OCT setup is based on the Mach–Zehnder type interferometer shown in Fig. 1. The light of a swept laser source (Superlum Broadsweeper BS 840, 50 nm sweep range, 841 nm central wavelength) is split into sample illumination and reference wave. The sample illumination beam contains 5.2 mW of radiation power. An achromatic lens creates a focus in the outside focal plane of the eye. Hence, the retina is illuminated by a collimated beam. The light backscattered by the retina is again collimated by the eye lens. After being limited by an adjustable aperture in the outside focal plane of the eye lens, the sample light is imaged onto the sensor of a high-speed camera (FASTCAM SA-Z, Photron), where it is superimposed with a reference wave incident at an angle of about 1.2° (off-axis geometry, see [9]). The central 896 × 368 pixels of the camera are read out at a frame rate of 60 kHz, acquiring 30 images during one wavelength sweep. That way perfectly phase stable OCT volumes are acquired with an effective A-scan rate of 660 MHz (135 MHz after off-axis filtering, 0.5 ms imaging time per volume). The number of images acquired per sweep can be increased to 512 for high-depth resolution imaging at 39 MHz A-scan rate; see, e.g., Fig. 2(c). A detailed description of the setup and applied data reconstruction is presented in [9].

To investigate vascular dynamics in the eye of a healthy subject, a 3.6 × 1.5 mm region 6 mm above the macula was measured [large yellow frame in Fig. 2(a)]. The pulsation characteristics of a large artery and vein located in that field of view were investigated, and the time delay of the pulsation in both vessels was determined. For the determination of pulse wave velocities, a mirrored prism and two telescopes were used to split the field of view on the retina into two 1.8 × 1.5 mm sized areas that are separated by a distance of about 12 mm [see Figs. 1(b) and 2(a)]. The exact distances the pulse waves have

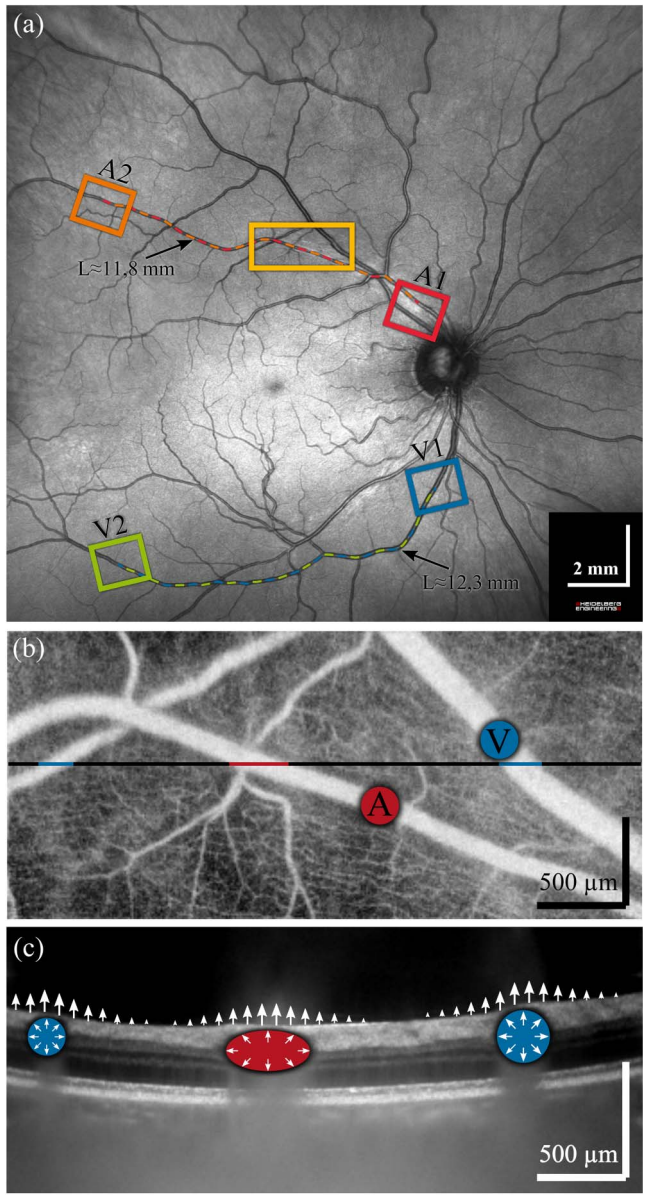

Fig. 2. (a) SLO image showing the investigated areas on the retina. The behavior of arterial and venous pulsations is analyzed in the region marked by the large yellow frame. Red/orange (A1/A2) and blue/green (V1/V2) frames indicate the two fields of view that were used for the measurement of arterial and venous PWV, respectively. (b) OCT angiography of the yellow framed area measured using FF-SS-OCT. The black line indicates the position of the B-scan shown in (c), where the measurement principle is demonstrated: The pressure-induced expansion of the vascular system causes axial motion of the surrounding tissue, which is measured by PhS-FF-SS-OCT.

to propagate along the marked vessels are 11.8 mm for the marked artery and 12.3 mm for the marked vein.

The acquired full-field spectra were processed as described in [9]. Using a cross-correlation of the OCT volumes, the global displacement of the retina due to pulsation and other motion of the eye was calculated and corrected by shifting the volumes accordingly. Afterward, the inter-volume phase differences $\Delta\phi^{(i)}(x, y, z)$ between each voxel (x, y, z) in the i^{th} volume and the corresponding voxel in the previous

$(i-1)^{\text{th}}$ volume were calculated. The phase differences of the retinal pigment epithelium $\Delta\phi^{(i)}(x, y, z_{\text{RPE}})$ and the nerve fiber layer $\Delta\phi^{(i)}(x, y, z_{\text{NFL}})$ were subtracted from each other and rescaled using the relation $\Delta z = \Delta\phi/2k_0$ to obtain the local axial expansion rate $\partial_t \Delta z^{(i)}(x, y)$ [see Fig. 2(c) for illustration]. Inherent to this calculation is the removal of any global phase shift due to potential inter-volume phase instability or motion of the patient. Even if the phase shift is larger than π and causes phase wrapping, this does not affect the calculation of the expansion rate, which is a purely differential motion. Afterward, a temporal integration of the expansion rate results in the time course of the local axial expansion $\Delta z^{(i)}(x, y)$. To increase the SNR, the obtained data are laterally averaged over about 40 μm using a Gaussian filter, which inevitably results in a corresponding decrease of lateral resolution.

The measured increase of the retinal thickness caused by the reversible expansion of the vessels during the cardiac cycle is shown in Fig. 3 and Visualization 1. Four complete cardiac cycles were measured within 3.75 s. The highest amplitude of retinal pulsation was measured in the tissue surrounding the large artery and vein. With increasing distance to the large vessels, the amplitude got smaller, but was still clearly visible, even in the capillary bed. To point out the different characteristics of arterial and venous pulsation, Fig. 4 shows the time course of retinal thickness changes measured at two spots at the artery and vein that are marked in Fig. 2(b). With systolic peak, dicrotic notch, and diastolic runoff, the well-known characteristics for arterial pulsation behavior were observed in the pulsation near the artery. In contrast, the venous pulsation has a smooth time course. To quantify this difference, both pulse curves were Fourier transformed. The frequency spectrum confirms that high-frequency components are less pronounced in the venous pulsation (see Fig. 5). The ratio of both Fourier spectra drops by more than one order of magnitude for frequencies above 5 Hz.

In addition to the different pulse shape, the pulsations near the artery and vein are slightly delayed to each other. The established methods to quantify this time delay can be separated into two groups: *foot-to-foot distance* and *filtered cross-correlation*. The foot-to-foot methods are based on a precise determination of the time of arrival of the pulse wave at two specific locations [10]. These methods generally provide

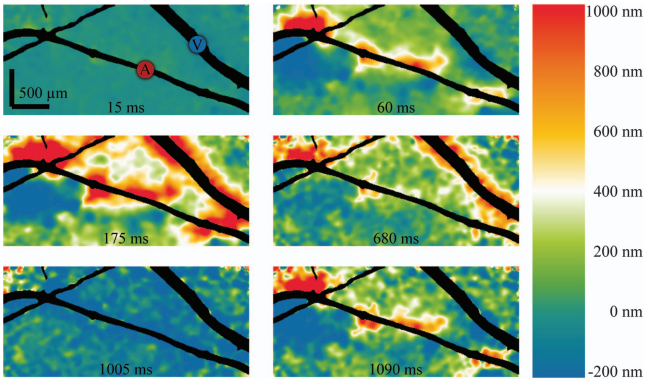

Fig. 3. Retinal thickness changes during four complete cardiac cycles are shown in Visualization 1. Here, six representative frames of the first cycle are shown. First the artery expands; then the vein follows. When the pulse wave has passed, the tissue returns to its initial state until the next pulse wave arrives.

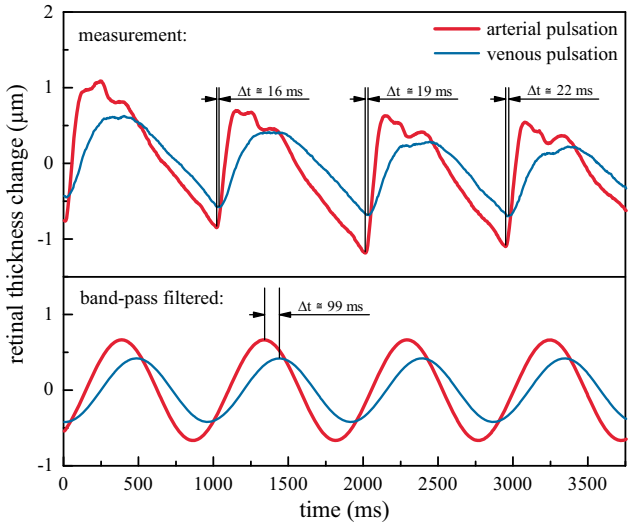

Fig. 4. Retinal pulsation near the artery and vein extracted at the locations indicated in Fig. 2(b). Additionally, the band-pass filtered pulsation is shown. The time delay between the band-pass filtered curves is 99 ms, while the foot-to-foot delay of the measured curves is just 19 ± 4 ms.

the most accurate results. However, they are only applicable if the pulsation can be resolved with a sufficiently high SNR. If the SNR is insufficient, filtered cross-correlation methods are applied. They estimate the time delay based on the phase shift of the pulsation curves after the raw data have been band-pass filtered at the cardiac frequency [1,3,7]. Different pulsation time delays were determined by employing the two methods: the foot-to-foot distance is 19 ± 4 ms, while filtered cross-correlation results in approximately 100 ms. Filtered cross-correlation methods overestimate the pulse propagation time because the actual impact of the pressure wave is predominantly determined by the high-frequency components. For the higher harmonics of the cardiac frequency, the time delay was determined to be about 20 ms using the phase differences of the complex Fourier spectra shown in Fig. 5. This is consistent to the previously determined foot-to-foot distance. At the cardiac frequency, however, a delay of about 100 ms is obtained, which is in accordance with the results obtained by filtered cross-correlation methods and the pulsation delays published in [11].

While the time delay between arterial and venous pulse is clearly visible, the propagation along the large vessels is obviously much faster than predicted by the RVA. If the PWV was 400 μm/s, then the peak-to-peak length of a pulse would be about 400 μm and, therefore, should be clearly visible in the 3.6 mm field of view. The measurement, however, definitely shows a peak-to-peak length far above 100 mm and, therefore, a minimum propagation speed of 100 mm/s, which is too fast to be measured within the 3.6 mm field of view. Therefore, additional measurements were carried out after splitting the field of view into two areas separated by about 12 mm using a mirrored prism and two telescopes [see Fig. 2(b)]. The two fields of view were then aligned to measure a proximal and a distal segment of the same artery; see red (A1) and orange (A2) frames in Fig. 2(a). The measured pulse curves are displayed in Fig. 6. Apart from the decreased amplitude in the distal segment, the pulse shapes were basically identical.

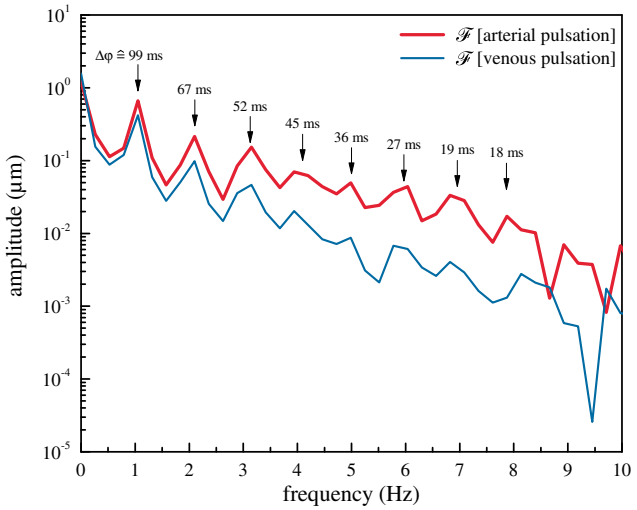

Fig. 5. Frequency spectra of the pulsation near the artery (red) and vein (blue). Additionally, the frequency-dependent time delay between arterial and venous pulsation is calculated using the corresponding phase differences of the Fourier spectra.

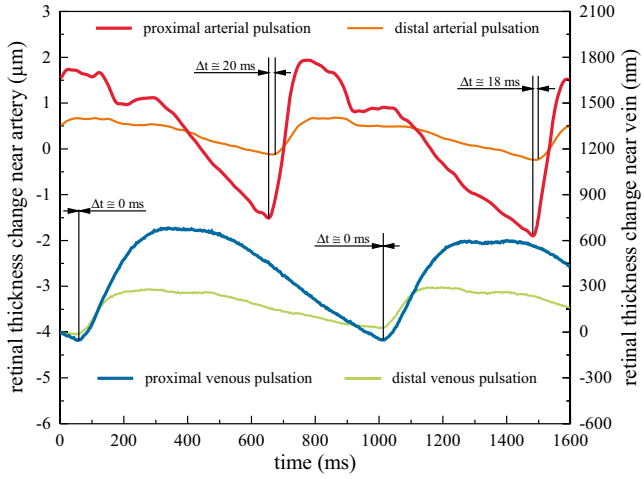

Fig. 6. Pulsation of a proximal and a distal segment of a large retinal artery and vein, respectively.

A Fourier analysis of the two pulse shapes revealed that the different frequency components were propagated at equal speeds of about 600 mm/s and constant amplitude ratio (data not shown). Therefore, both methods of PWV determination were in good accordance to each other: the PWV was consistently determined to be 620 ± 50 mm/s. This is about 1,500 times faster than expected from recently published data of retinal PWV measured using the RVA [1]. Given the PWV determined in animal studies [4–6] and in the human vascular system [10], as well as the theory of pulse propagation [2], our results seem much more realistic.

To determine the PWV in a retinal vein, the two fields of view were aligned accordingly. However, no time delay between the pulsations of the two venous segments [Fig. 2, blue (V1) and green (V2) frame] was observed; see Fig. 6. Hence, the venous pulsation does not propagate along the vessel in the same way as the arterial pulse wave. This can be explained by the fact that the cardiac pressure wave enters the artery at one single position. The vein, however, is entered by many pulse waves at a very large number of venules that are more or less evenly distributed over the length of the vessel. Furthermore, due to the different pathways that the pulse waves have covered, they interfere with different time delays. Therefore, no propagation of a single pressure wavefront can be observed in veins, and the high-frequency components of the pressure pulse cancel out because of phase washout.

In conclusion, PhS-FF-SS-OCT allows high-speed imaging of retinal vascular dynamics with unprecedented temporal resolution and perfect phase stability. The motion of retinal tissue that is induced by expansion of the vessels therein is measured with an accuracy of about 10 nm. The potential of this imaging method is demonstrated by investigating the arterial and venous pulsation behavior and the pulse propagation through the capillary bed. For the first time, direct measurements of pulse waves propagating with more than 600 mm/s in retinal vessels of a healthy young subject are demonstrated. Future work will include investigations of patients with cardiovascular diseases to evaluate PhS-FF-SS-OCT for a noninvasive determination of biomechanical properties of the retinal vascular system and the surrounding tissue. Since previously published results are contradictory, a detailed investigation of pulse wave propagation in the retinal vascular system is needed to fully understand the observations made using the RVA and FF-SS-OCT. Furthermore, FF-SS-OCT may be used to measure optophysiological effects and thermal expansion during photocoagulation treatment.

REFERENCES

1. K. Kotliar, H. Hanssen, K. Eberhardt, W. Vilser, C. Schmaderer, M. Halle, U. Heemann, and M. Baumann, Microcirculation **20**, 405 (2013).
2. A. I. Moens, "Over de voortplantingssnelheid van den pols (On the propagation of pulse)," Ph.D. thesis (S.C. Van Doesburgh, 1877).
3. T. Otto, "Modellierung des retinalen Blutflusses durch Auswertung bewegungskorrigierter Angiographie-Bildfolgen (Parametrization of the retinal blood flow by analysis of motion compensated angiography image sequences)," Ph.D. thesis (University of Heidelberg, 2000).
4. C. Yeh, S. Hu, K. Maslov, and L. V. Wang, J. Biomed. Opt. **17**, 070504 (2012).
5. J. Seki, Am. J. Physiol. **266**, H811 (1994).
6. S. M. Golzan, M. Butlin, Z. Kouchaki, V. Gupta, A. Avolio, and S. L. Graham, Microvasc. Res. **92**, 56 (2014).
7. K. Kotliar, M. Baumann, W. Vilser, and I. M. Lanzl, Br. J. Ophthalmol. **95**, 675 (2011).
8. L. An, J. Chao, M. Johnstone, and R. K. Wang, Opt. Lett. **38**, 1512 (2013).
9. D. Hillmann, H. Spahr, H. Sudkamp, C. Hain, L. Hinkel, G. Franke, and G. Hüttmann, "Off-axis full-field swept-source OCT and holoscopy," Opt. Express (in preparation).
10. O. Vardoulis, T. G. Papaioannou, and N. Stergiopulos, Am. J. Physiol. **304**, H1558 (2013).
11. K. Gugleta, A. Kochkorov, R. Katamay, C. Zawinka, J. Flammer, and S. Orgul, Invest. Ophthalmol. Visual Sci. **47**, 4019 (2006).