

Comparative Study of Optical Coherence Tomography Angiography and Phase-Resolved Doppler Optical Coherence Tomography for Measurement of Retinal Blood Vessels Caliber

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Received: 8 May 2018

Accepted: 12 July 2018

Published: 24 August 2018

Keywords: doppler optical coherence tomography; optical coherence tomography angiography; retinal imaging; ocular perfusion pressure

Citation: Hosseinaee Z, Tan B, Martinez A, Bizheva KK. Comparative study of optical coherence tomography angiography and phase-resolved doppler optical coherence tomography for measurement of retinal blood vessels caliber. *Trans Vis Sci Tech.* 2018;7(4):18, <https://doi.org/10.1167/tvst.7.4.18>
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Purpose: To compare the accuracy of Doppler optical coherence tomography (DOCT) and OCT angiography (OCTA) for measuring retinal blood vessel caliber at different flow rates.

Methods: A research-grade 1060-nm OCT system with 3.5- μm axial resolution in retinal tissue and 92,000 A scan/s image acquisition rate was used in this study. DOCT and OCTA measurements were acquired both from a flow phantom and in vivo from retinal blood vessels in six male Brown Norway rats. The total retinal blood flow (TRBF) was modified from baseline to 70% and 20% of baseline by reducing the ocular perfusion pressure (OPP). The retinal blood vessel caliber (RBVC) was measured from OCTA and DOCT images. The caliber measurements were conducted by two separate graders using a custom MATLAB-based image processing algorithm.

Results: The RBVC measured with OCTA and DOCT for normal blood flow rates were not significantly different (56.69 ± 12.17 and $57.17 \pm 9.46 \mu\text{m}$, $P = 0.27$, respectively). However, significant differences were detected when TRBF was reduced to 70% (55.69 ± 11.56 vs. $50.62 \pm 8.85 \mu\text{m}$, $P < 0.01$) and 20% (50.29 ± 9.29 vs. $44.88 \pm 7.13 \mu\text{m}$, $P < 0.01$) of baseline.

Conclusions: Reduced TRBF resulted in inaccuracy of the RBVC measurements with DOCT in both the phantom and animal study. This result suggests that OCTA is a more accurate tool for RBVC evaluation when applied to retinal diseases associated with reduced TRBF, such as glaucoma and diabetic retinopathy.

Translational Relevance: Results from this study are directly applicable to clinical studies of retinal blood flow measured with OCTA and DOCT.

Introduction

Retinal blood vessel caliber (RBVC) is a metric with potential relevance to the diagnostics and monitoring the treatment of various ocular vascular-related diseases, such as age-related macular degeneration, retinal vein occlusion, diabetic retinopathy, and open-angle glaucoma.^{1–3} As such, precise evaluation of the RBVC is clinically important. Previously, various label-free angiographic methods

have been used for in vivo measurements of RBVC, such as fundus photography,⁴ retinal vessel analyzer (RVA),⁵ scanning laser ophthalmology,⁶ and retinal oximetry.^{7,8} However, those methods have multiple disadvantages or limitations, including complex system design, poor reproducibility of the vessel caliber data, and significant variation in the measured parameters. Optical coherence tomography (OCT) is an imaging modality that has been used for clinical diagnostics and management of various retinal

diseases for the past 2 decades.^{9–11} OCT offers high spatial resolution, noninvasive imaging, and high-image acquisition rates, which allows for large field of view and cellular resolution imaging of the morphology of biological tissues. In the past, a number of studies have been conducted to measure the blood vessel caliber from cross-sectional OCT B-scans^{12–18} or the shadow profiles of blood vessels.¹⁹ Specifically, Ouyang et al.¹⁷ used OCT cross-sectional images for measuring RBVCs in a clinical study, and showed high correlation with data acquired with an infrared reflectance (IR) imaging system. Muraoka et al.¹⁸ used a commercial OCT system to evaluate the effect of age and hypertension on the RBVC in humans. Results from that study showed significant thickening of the retinal vessel wall associated with aging and hypertension. Phase-resolved Doppler OCT (DOCT) and OCT angiography (OCTA) use phase information in the OCT fringes, and therefore can create vascular maps of higher sensitivity compared with those created from morphologic OCT images that use only the intensity of the OCT fringes.

Over the past 10 years, researchers have investigated the feasibility of blood vessel caliber measurement by DOCT and OCTA, and compared these two methods with previously applied clinical methods. For example, Falavarjani et al.²⁰ compared RBVCs measured in OCTA images with color fundus photography. Although their results showed high correlation between the RBVCs measured with the two methods, the OCTA data showed consistently higher values for the RBVCs relative to the fundus photography data. Fondi et al.²¹ compared RBVCs measured with DOCT and RVA and their study showed that RBVCs measured from the DOCT images were consistently and significantly smaller than those measured by RVA. Doblhoff-Dier et al.²² used DOCT images for measuring RBVCs smaller than 65 μm in a clinical study, and also compared the RBVCs measured by OCT images to that measured by dynamic vessel analyzer (DVA), their results showed that due to the approximate parabolic profile of the flow and very high absorptive nature of the blood, which results in shadowing effects behind the vessel, the retinal blood vessel caliber will be underestimated if extracted from OCT phase images, and proposed an average underestimation factor of 14% compared with DVA results.

All the translational preclinical studies mentioned above aimed to compare other RBVC modalities to DOCT or OCTA images; however, no study has been conducted to compare the accuracy of DOCT and

OCTA for measurement of RBVC. Because the accuracy of measuring RBVC is based on the vessel contrast in the images, the difference in the contrast mechanisms between DOCT and OCTA could result in different sensitivity to vessel morphology detection. The purpose of this study was to compare the accuracy of phase-resolved DOCT and OCTA for measuring retinal blood vessel caliber at different flow rates. In order to accomplish this task, we conducted a phantom study and an in vivo animal study, where the flow rate was controlled by a syringe pump in the phantom study, and the total retinal blood flow (TRBF) was changed by modifying the OPP in the animal study. Some of the preliminary results from this study were presented at the 2017 Conference on Vision and Imaging Systems, Waterloo, Canada.²³

Methods

System Setup

A research-grade spectral-domain OCT system was used in this study²⁴. Briefly, the OCT system operates in the 1060-nm spectral region and provides approximately 3.5- μm axial and 5- μm lateral resolution in the rat retina. The system's sensitivity was measured to be approximately 100 dB for 1.7-mW optical power of the imaging beam incident on the cornea and 92,000 A scans/s image acquisition rate. At this image acquisition rate, the resultant blood flow velocity detection range of the OCT system was [−17.4, 17.4] mm/s without phase unwrapping.

Phantom Study

For the phantom study, we used glass capillary with inner diameter of 100 μm (Charles Supper Company, Inc., Natick, MA), comparable to larger blood vessels in the rat retina. The capillary was filled with milk (18% diluted in water 1:5). The flow rate was controlled by a syringe pump (New Era Pump Systems, Inc., Farmingdale, NY), and for this study, the pump speed was increased linearly from 10 to 40 $\mu\text{L}/\text{min}$ with 5- $\mu\text{L}/\text{min}$ interval. The Doppler angle between the OCT imaging beam and the glass capillary was set to 10°. For each flow velocity, both OCTA and DOCT data were collected from an area of 0.8 \times 0.8 mm with the following data acquisition protocols: 400 A-scans \times 400 positions \times 4 scans/position for the OCTA data sets, and 2000 A-scans \times 200 B-scans for DOCT data sets. Figure 1, shows enface OCTA image from the glass capillary (Fig. 1A), and the corresponding DOCT image (Fig. 1B).

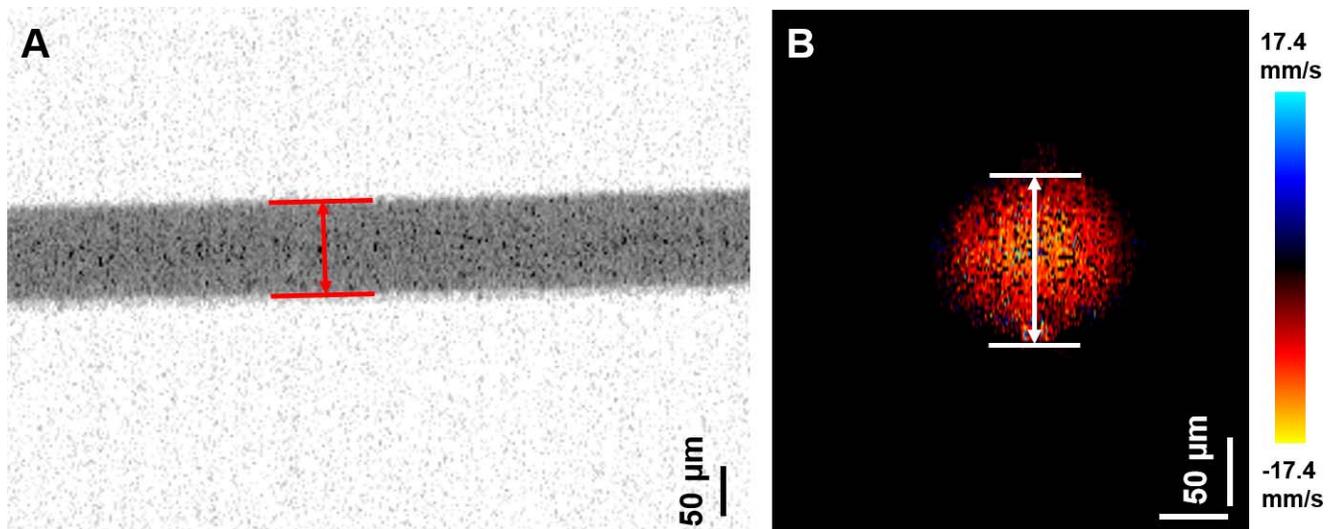


Figure 1. Glass capillary phantom caliber measurements, (A) en face OCTA image acquired at 25- μ L/min flow velocity. (B) Corresponding DOCT B-scan.

The glass capillary size measured from the OCTA image was corrected to compensate for the refractive index's difference between air and the glass of the capillary wall.

Animal Study

Eleven-week-old male Brown Norway rats (\sim 300 g) were used in the *in vivo* study ($n = 6$). All experiments described here were approved by the University of Waterloo Animal Research Ethics Committee and adhered to the ARVO statement for Use of Animals in Ophthalmic and Vision Research. The rats were anesthetized with isoflurane and oxygen mixture maintained at 1.5% to 2.5% throughout the experimental procedures. A customized animal holder that allowed for XYZ translation and angular rotation was used to align the animal eye relative to the stationary OCT imaging probe. A thermal pad (Kent Scientific, Torrington, CT) was used to keep the rat body temperature between 36°C and 38°C. One drop of 0.5% proparacaine hydrochloride (Alcaine, Alcon, Mississauga, ON, Canada) was applied to each eye, followed by one drop of pupillary dilator (0.5% tropicamide; Alcon). In order to provide different flow rate, the OPP was reduced to the outside of the autoregulation boundary by increasing the intraocular pressure (IOP). An adjustable vascular loop (Sentinel Loops; Sherwood-Davis and Geck, St. Louis, MO) was placed anterior to the equator of the eyeball of the right eye to provide controllable IOP elevations, while the left eye served as a contralateral control. Topical anesthesia (0.5% proparacaine hy-

drochloride, Alcaine Alcon) was applied onto the cornea to reduce the rats' sensation to the vascular loop. Different IOP levels were achieved by manually adjusting the tightness of the vascular loop, and the IOP was measured with a precalibrated corneal rebound tonometer (TonoLab, Vantaa, Finland). The IOP was raised unilaterally from baseline (\sim 10 mm Hg) to 30 and 50 mm Hg that, based on our previous studies,²⁵ was expected to reduce the TRBF to approximately 70% and 20% of the baseline value. At each IOP level, the rats were stabilized for approximately 10 minutes and the IOP was measured 3 times prior to the monocular OCT recordings. The treated eye was always imaged before the control eye. Systemic blood pressure was measured by a tail cuff (CODA surgical monitor; Kent Scientific, Torrington, CT). OCTA images were acquired around the optical nerve head (ONH) (3.4 mm \times 3.4 mm; 512 A-scans \times 512 positions \times 4 scans/position). Doppler OCT images were acquired from a relatively smaller area centered at the ONH with dense scanning pattern (2 mm \times 2 mm, 3000 A-scans \times 200 B-scans). Note that the requirement of large number of A-scans and limiting the total image acquisition time to less than 10 seconds has resulted in a smaller imaged area in the case of the DOCT measurement.

Image Processing

In the animal study, the area imaged with the OCTA protocol was \times 1.7 larger than the area imaged with the DOCT protocol, and a custom cross-correlation algorithm (MATLAB; MathWorks, Na-

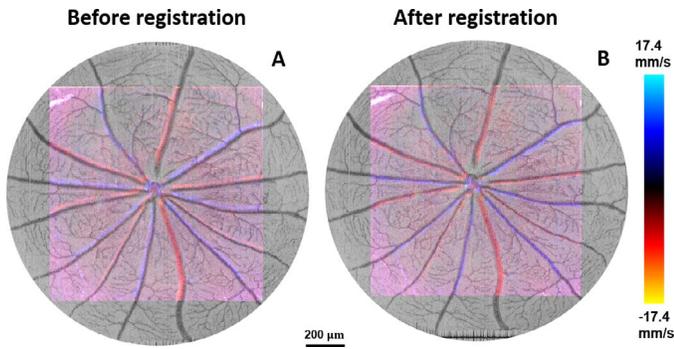


Figure 2. Overlaid DOCT image and OCTA image before/after application of the cross-correlation registration.

tick, MA) was developed to register the maximum projected DOCT image to the maximum projected OCTA image (Figs. 2A, 2B). For each blood vessel, calibers from two different locations (400 and 600 μm away from the center of the ONH, which was selected manually as the converging point of major retinal arteries) were evaluated manually by two independent graders (ZH and AM). Figure 3 shows the procedure

of a RBVC measurements, in the OCTA image, the measurement of the RBVC was conducted from the maximum projected en face view, while in the DOCT image, the retinal blood vessel caliber was determined as the diameter of the vessel's cross section.

TRBF was evaluated using the Doppler angle independent en face method proposed by Srinivasan et al.,²⁶ where the blood flow is computed as the integration of the axial velocity over the blood vessel's area from an en face scan. TRBF of the retina was calculated as an average of the absolute total venous and arterial flow around the ONH.

Statistical Analysis

Paired sample *t*-test was used to determine any differences between arterial and venous calibers and compare the RBVC measured by the OCTA and DOCT. One-way ANOVA was used to determine the difference between RBVC at different OPP levels. The agreement between the two graders was analyzed using linear correlation analysis (Pearson correlation

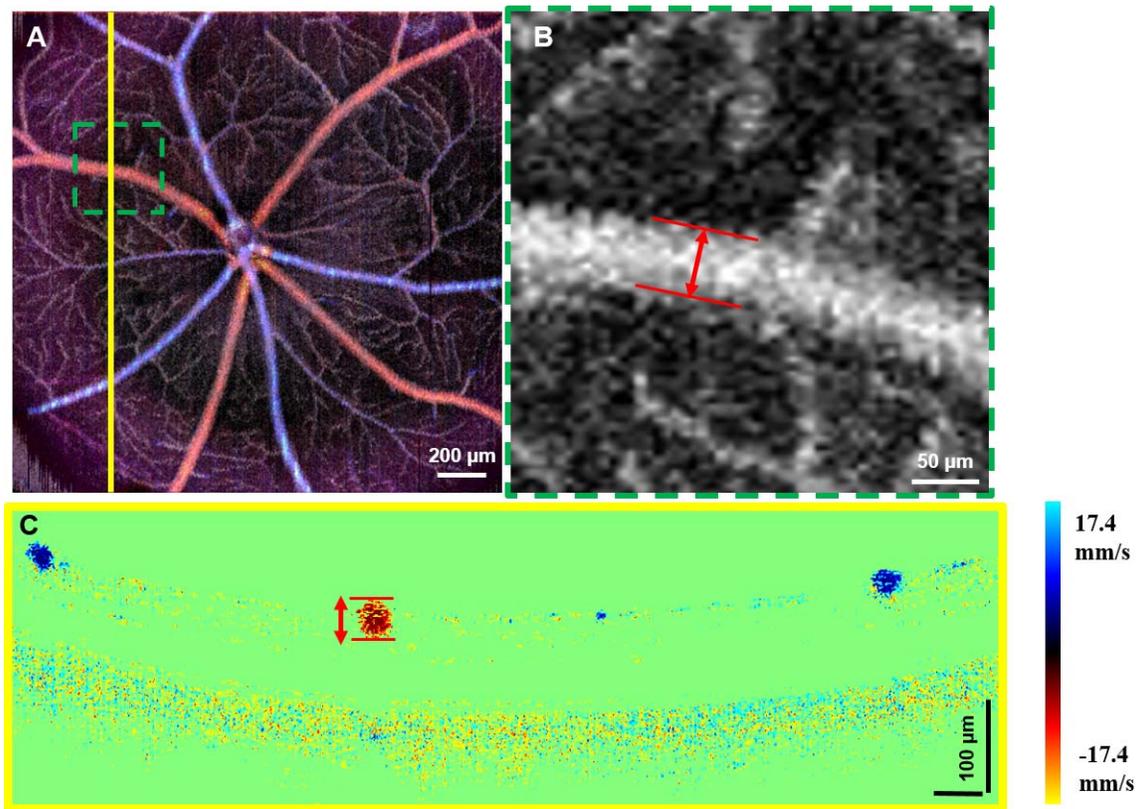


Figure 3. Measurement of the retinal blood vessel caliber from a presentative en face OCTA image and DOCT image. (A) Overlaid en face DOCT and OCTA images after registration. (B) Magnified view of the arear in 3A marked with the *green dashed square* that illustrates the measurement of RBVC from an OCTA en face image. (C) The corresponding DOCT B-scan (location labelled with the *yellow line* in [A], to illustrate the measurement of the RBVC).

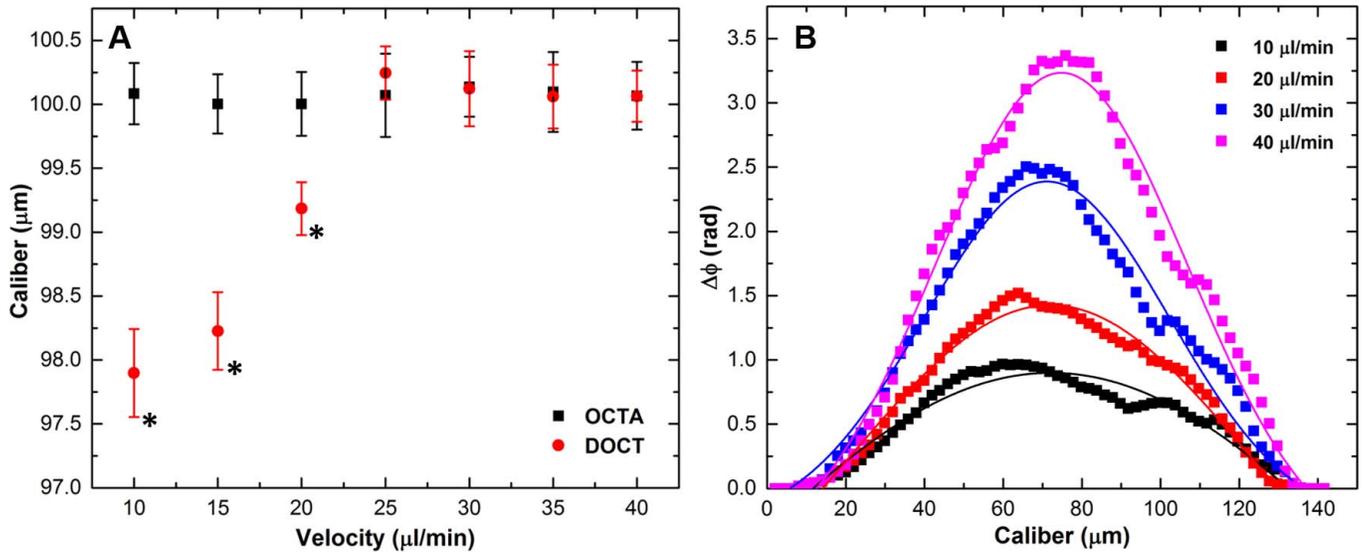


Figure 4. (A) Calibers measured from both OCTA and DOCT images at different flow rates. *Significant difference between the glass capillary calibers measured by OCTA and DOCT. Data are presented as Mean ± SD. (B) Phase differences across the capillary phantom for different flow rates.

coefficient). Additionally, Bland-Altman plots were generated to show the frequencies of relative difference between the two methods. $P < 0.05$ was considered to be statistically significant. All data are reported as mean ± standard deviation (SD).

Results

Phantom Study

Figure 4A shows the calibers of the glass capillary measured by both OCTA and DOCT at different flow rates. It is evident that the caliber measured by OCTA is consistent over the different flow rates ($100.06 \pm 0.26 \mu\text{L}/\text{min}$). There is no significant difference between the calibers measured by OCTA and DOCT when the flow rate is equal to or higher than $25 \mu\text{L}/\text{min}$. However, significant differences are detected when the flow rate is equal or lower than $20 \mu\text{L}/\text{min}$ ($P < 0.01$ for all comparisons) with the difference being higher for the lower flow rates. Specifically, for flow rate of $15 \mu\text{L}/\text{min}$, the DOCT measured caliber is approximately 2.5% smaller than the caliber measured by OCTA. Figure 4B shows the axial flow velocity profile across the glass capillary from the DOCT data for different flow rates. The detected profiles are fitted with a parabolic function, as the flow in the capillary is slow enough to be considered laminar. Progressive increase of the maximum flow velocity is observed with increasing pump flow rate,

resulting in higher signal-to-noise ratio (SNR) in the DOCT images (data not shown).

Animal Study

The agreement between the two graders (ZH, AM) for measuring RBVCs from the OCTA and DOCT images were evaluated based on Pearson correlation coefficients, and the calculated value was approximately 0.95 for both the OCTA and DOCT data, suggesting excellent agreement between the two graders. Figure 5 shows the correlation of calibers measured by the 2 graders for the OCTA and DOCT data separately. Each grader has completed 177 caliber measurements from 89 retinal vessels from the OCT images acquired at baseline (normal TRBF). Each grader also conducted 84 caliber measurements from 40 retinal blood vessels from the reduced TRBF data, for each of the IOP elevation values (30 and 50 mm Hg). Therefore, the total number of caliber measurements carried out by each grader is 345. From here, the reported RBVCs are the averaged value from the two graders.

Figure 6 summarized the RBVCs measured from the DOCT and OCTA images for the different TRBF. Red squares and blue circles mark the retinal veins and arteries respectively. Overall, the venal calibers were generally larger than the arterial calibers for all retinal flow rates ($P < 0.01$) and measured from both the DOCT and the OCTA images. The Table

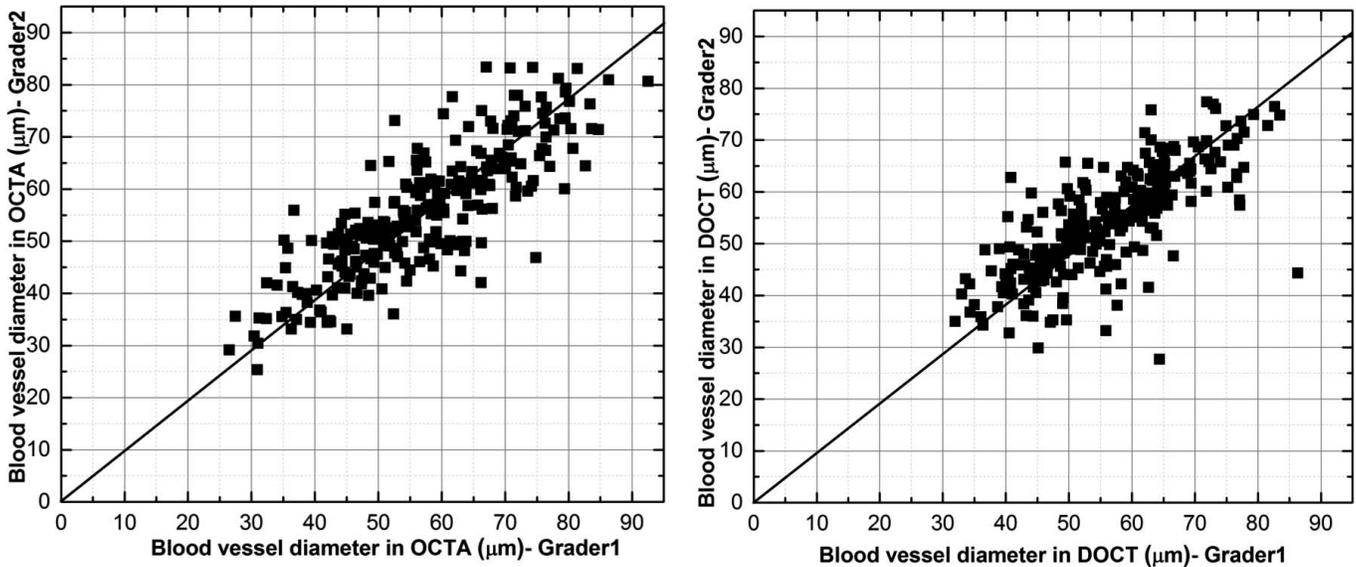


Figure 5. Correlation of vessel calibers measured by both graders on OCTA and DOCT images. Total number of samples is 345, measured at baseline and at increased OPP levels.

summarizes the RBVCs measured by OCTA and DOCT images at different OPP levels. At normal TRBF, RBVCs measured by OCTA and DOCT were not significantly different (56.83 ± 13.37 vs. $56.23 \pm 10.82 \mu\text{m}$, $P = 0.5$). When the OPP was reduced to 70 mm Hg, the TRBF was reduced to 70% compared with baseline. The RBVC measured by OCTA and DOCT decreased significantly compared with the baseline ($55.69 \pm 11.56 \mu\text{m}$, $P = 0.1$; $50.62 \pm 8.85 \mu\text{m}$, $P < 0.01$), and RBVC measured from DOCT is significantly smaller than RBVC measured from OCTA ($P < 0.01$). When the OPP was further reduced to 50 mm Hg, the TRBF decreased sharply

to approximately 25% compared with baseline. Again, the RBVCs measured by OCTA and DOCT decreased significantly compared with the 70 mm Hg OPP ($50.29 \pm 9.29 \mu\text{m}$, $P < 0.01$; $44.88 \pm 7.13 \mu\text{m}$, $P < 0.01$), and the RBVC measured from DOCT were significantly smaller than the RBVC measured from OCTA ($P < 0.01$). Bland-Altman plots for comparing RBVC measured by DOCT and OCTA are shown in **Figure 7**. The data points are shown separately for arteries and veins at baseline and decreased flow rates. Evidently, veins are slightly larger than arteries, and the RBVC measured from DOCT is smaller than the RBVC measured from OCTA for reduced TRBF.

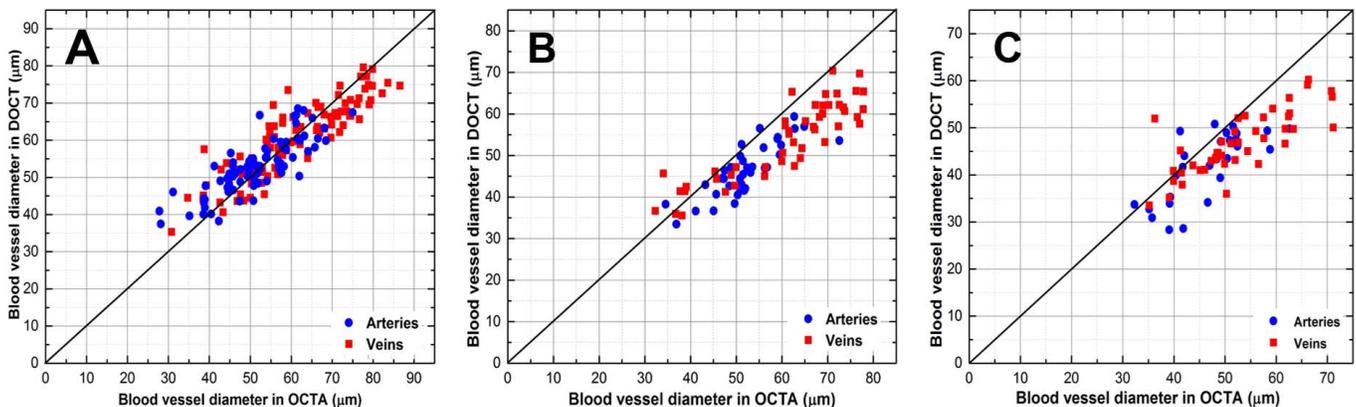


Figure 6. Comparison of RBVC measured by DOCT and OCTA for different OPP levels: (A) baseline level of 100 mm Hg; (B) 70 mm Hg; (C) 50 mm Hg.

Table. RBVC Measured From DOCT and OCTA Images for Different OPP Values

Vessel Diameter	Sample Size	OCTA, μm	DOCT, μm	P Value
Arteries (baseline)	81	51.45 \pm 9.46	52.94 \pm 7.39	0.01*
Veins (baseline)	96	61.12 \pm 12.48	60.75 \pm 9.90	0.5
Arteries (70 mm Hg)	37	52.18 \pm 7.450	46.53 \pm 6.38	<0.01*
Veins (70 mm Hg)	47	56.63 \pm 13.78	52.13 \pm 10.20	<0.01*
Arteries (50 mm Hg)	37	46.08 \pm 7.54	42.46 \pm 4.82	<0.01*
Veins (50 mm Hg)	47	51.67 \pm 10.12	47.17 \pm 5.65	<0.01*

Data are presented as Mean \pm SD.

Discussion

In the phantom study, the calibers measured from the OCTA images were not significantly different from the physical inner diameter of the glass capillary (100 μm) for all different flow rates that were tested. However, our study shows that the DOCT images have a tendency to underestimate the vessel calibers at flow rates lower or equal to 20 $\mu\text{L}/\text{min}$. This results is in agreement to a similar study conducted by Greenleaf et al.²⁷ One possible explanation for this effect is that for laminar flow, the flow velocity profile is close to a parabolic function with the flow velocity near the capillary wall being at its minimum. For slow flow rates, the phase difference generated by velocities near the vessel wall can be close to the phase noise floor of the OCT system, thus leading to underestimation of the blood vessel's diameter in DOCT images.

In the animal study, the RBVCs measured from the DOCT data are significantly smaller than the RBVC measured from the OCTA data for the low retinal blood flow rates. Similar to the phantom study, one possible reason is due to the reduced phase contrast of the vessels boundaries at the reduced flow

rates. Note that the shape of the blood vessel is not necessarily round, and by increasing the IOP, the shape of the retinal vessels could become more elliptical in the transverse direction, which contributes partially to the difference observed in the caliber measurements in axial direction (DOCT) and transverse direction (OCTA).

Furthermore, the RBVCs measured at reduced OPPs were significantly smaller than those measured at baseline level. The retinal blood vessel autoregulatory procedure dilates the retinal vessel caliber to ensure oxygen and metabolic supply to the retinal tissue at low OPPs. When OPP is further reduced to beyond the autoregulation region, retinal ischemia can cause impaired vessel dilation and result in reduced RBVCs.²⁸ In our study, reduced retinal blood flow correlates well with the reduced RBVCs when the OPP was reduced to 70 mm Hg and less. It was also shown in an animal study conducted by Zhi et al.²⁹ that the retinal vessel caliber decreased, although not significantly, at 50 mm Hg IOP measured from OCTA. In a clinic study,³⁰ IOP in human eyes was raised acutely to 43 mm Hg by suction cup and significant decrease of the retinal blood vessel caliber was reported using retinal vessel

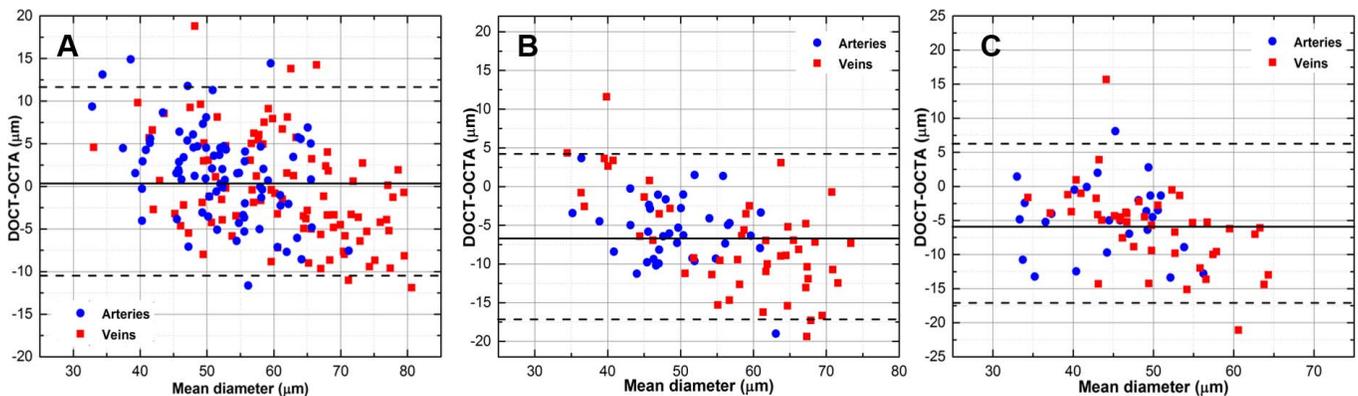


Figure 7. Bland-Altman plots comparing arterial and venal calibers measured by OCTA and DOCT for different OPP levels: (A) baseline, (B) 70 mm Hg, (C) and 50 mm Hg. Red squares represent retinal veins and blue circles represent retinal arteries.

analyzer. The direct quantitative comparison between these two studies and our studies needs care because of with/without anesthesia³¹ and different IOP elevation approaches.

Another interesting observation of our study was that, reduced OPP has more pronounced effect in decreasing venal calibers than arterial calibers (Table). The retinal circulation can be modeled as a Starling resistor,³² where the pressure gradient starts from the arterial pressure and finishes with venous pressure. Reducing OPP by increasing IOP will therefore increase the distal pressure of the resistor and the resistance of the flow, in another words, will increase the venal pressure. Therefore, IOP elevation has more pronounced effect on the veins compared with arteries, resulting larger caliber decreases. Moreover, this effect can also be explained by thinner walls and lower intraluminal pressure in veins.³³

One limitation of our study is the lack of clinic data. To translate this study to human subjects, certain modifications are needed. Unlike the animal study where stereotaxical instruments and anesthesia are used for reduced bulk motion, motion artifact including head motion, cardiac pulsation, and involuntary eye motion will compromise the quality of the images. Fast cameras and altering the image acquisition protocols (e.g., reduce repeated B scan number to 2 in OCTA) could partially suppress motion artifacts in the DOCT and OCTA images. Faster image acquisition rates will also reduce the potential phase wrapping associated with faster retinal blood flow speed that is typical for the human eye compared with blood flow in the rat retina.

In summary, this study compared and evaluated the possibility of using OCTA and DOCT images for measuring RBVC. Results from both the phantom and animal studies showed that at reduced flow rates, DOCT has a tendency to underestimate the vessel calibers. Further studies will be conducted to investigate the feasibility of OCTA and DOCT in measuring RBVC on healthy human subjects and subjects with reduced retinal flow associated with retinal diseases, such as glaucoma.

Acknowledgments

The authors would like to thank Nancy Gibson and Jean Flanagan for assistance with the animal-related procedures, and Harmen Vander Heide for assistance with the design of the custom stereotactic animal holder.

This project was funded by the Natural Sciences and Engineering Research Council of Canada and the Canadian Institutes of Health Research (NSERC-312037 and CIHR-446387) and the University of Waterloo Research Incentive Fund.

Disclosure: **Z. Hosseinaee**, None; **B. Tan**, None; **A. Martinez**, None; **K.K. Bizheva**, None

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