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# Prospective Cross-sectional Study of Repeatability of Peripapillary Capillary Density Measurement using Optical Coherence Tomography Angiography in Eyes with Optic Nerve and Retinal Vascular Pathology

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**Keywords**

optical coherence tomography angiography; optic disc atrophy; optic disc edema; papilledema; radial peripapillary capillary density; repeatability

Optical coherence tomography angiography (OCTA) is a new non-invasive imaging modality that generates high resolution 3-dimensional vascular flow images of the posterior segment. As such, OCTA has been useful in characterizing retinal and choroidal vascular flow changes associated with common retinal diseases such as diabetic retinopathy or macular degeneration.[1–3]

More recently OCTA has been used to evaluate and quantitate the vessel density in the peripapillary region. Commercial OCTA instruments provide clinicians with high-resolution images of the peripapillary retinal capillary network.[4] Various groups have noted changes in the peripapillary capillary density in eyes with glaucoma[5–9] or retinal vascular occlusions.[2] A few studies have also demonstrated areas of decreased peripapillary vessel density in

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eyes with optic atrophy or disc edema from non-arteritic ischemic optic neuropathy and papillitis.[10,11]

With development of software to quantitate the peripapillary vessel density, these changes can be evaluated in detail and may be useful in diagnosing optic neuropathy.[12] However, the changes can vary depending on the software used. Two studies used an early version of Optovue OCTA software and noted a lower peripapillary capillary density in eyes with papilledema which was not noted using a custom software that removes larger vessels.[11,12]

The Optovue AngioVue OCTA (RTVue XR, Avanti, Optovue, Inc, Fremont, CA) was the first commercially available OCTA device. The OCTA software used in earlier studies has been updated and the current version (Version 2018.0.0.1) is the only FDA-approved commercial OCTA software to quantify the peripapillary vascular density to date. The Optovue optical coherence tomography (OCT) instrument uses an 840nm light source and camera that captures 70,000 A-scans per second with the aid of live tracking during scan capture. The OCTA software uses split-spectrum amplitude-decorrelation angiography (SSADA) algorithm to detect movement (ie. bloodflow) and subtracts out the larger blood vessels to calculate the radial peripapillary capillary (RPC) density, a measure of peripapillary vascular density.[13]

In order to determine whether the RPC measurement is a reliable OCTA measure that can be used for diagnosis and clinical evaluation, it is important to determine whether the measurement is repeatable in both normal eyes and eyes with anatomic changes associated with optic neuropathy or retinal vasculopathy. Prior studies have noted high repeatability of the peripapillary vascular density measurement in normal eyes and eyes with glaucomatous optic disc cupping.[14–16] However, the repeatability of the peripapillary vascular density measurement in eyes with disc edema, optic atrophy, or retinal vasculopathy has yet to be determined.

In this study, we hypothesize that the measurements of the RPC density using the commercial OCTA instrument, Optovue RTVue, with the latest software is highly repeatable in eyes with disc atrophy, disc edema, or retinal vasculopathy and comparable to that observed in normal eyes. The results of this study will help elucidate whether the RPC measurements of various peripapillary capillary zones are reliable and repeatable in eyes with optic nerve and retinal pathologies.

## Methods

### Study Population

This prospective cross-sectional study was performed in accordance to a study protocol approved by the Institutional Review Board of the University of California Davis Office of Human Research and in adherence to the Declaration of Helsinki for research involving human subjects. Patients seen at the University of California Davis Eye Center for standard of care between October 27, 2017 and May 23, 2018 were recruited if they satisfied the study criteria. A written informed consent was obtained before study enrollment. Inclusion criteria included diagnosis of optic disc edema or atrophy with or without a contralateral

normal eye or retinal vasculopathy without optic neuropathy, best-corrected visual acuity ≥ 20/200, and at least 18 years of age. Exclusion criteria included other concurrent retinal or optic nerve conditions affecting vision, significant media opacity, pregnancy, head tremor, and other factors precluding proper fixation and head immobilization during OCT imaging.

### Imaging Protocol

After pupil dilation and a comprehensive eye examination, each subject was imaged twice per eye on the same day, 30 minutes apart, using Optovue RTVue XR Avanti (Version 2018.0.0.1) OCTA instrument. An experienced OCTA technician with certification to perform OCT imaging for clinical trials obtained two 4.5mm x 4.5mm OCTA images of the optic disc. All OCTA images were reviewed for proper centration, and image quality of 6 or greater was considered good. The automated measurements of the RPC density were obtained using the OCTA imaging software (Figure 1). More specifically, the software calculated the capillary density as the proportion of A-scans representing vessels less than 3 pixels in width, subtracting out the larger blood vessels using a binary mask. The RPC density (%) is the percentage of the en face OCTA scan image obtained between the internal limiting membrane (ILM) and posterior boundary of the nerve fiber layer (NFL) where vascular flow is detected.

### Statistical Analysis

Automated measurements of various RPC density data for small vessels were collected for statistical analysis. These parameters include the RPC density (%) of the whole 4.5 × 4.5 mm image, inside the disc, of the peripapillary region, and each peripapillary quadrant (superior, nasal, inferior, temporal). A two-tailed Student's t-test was used to compare means. The method of Benjamini, Hochberg, and Yekutieli was used to adjust p-values for multiple comparisons. A p-value of ≤ 0.05 was considered statistically significant. The intraclass correlation coefficients (ICC) were calculated using a random effects model with random effects eye and patient to determine the repeatability of each parameter. An ICC of 0.5 or less is considered poor repeatability, 0.5 to 0.75 as moderate repeatability, 0.75 to 0.90 as good repeatability, and >0.90 as excellent repeatability. 95% confidence intervals were calculated to convey the precision of the ICC values.

## Results

Table 1 summarizes the demographic and clinical features of the patients included in this study. After excluding one patient due to poor centration of the OCTA scan (patient had optic atrophy in the setting of a pituitary adenoma), a total of 31 subjects were included in the data analysis as the total cohort. Of these patients, three contralateral eyes were excluded (one with glaucoma, one with a failed corneal graft, and one with poor centration in the setting of grade 3 papilledema), yielding a total of 59 eyes for our study. The total cohort included 9 eyes with disc edema from papilledema (grade 2 or less), 7 eyes with optic atrophy, 35 eyes with retinal vasculopathy, and 8 normal eyes. The subgroup of eyes (40 eyes) that had high quality OCTA images for both OCTA scans (i.e. image signal ≥ 6), included 7 eyes with disc edema from papilledema, 4 eyes with disc atrophy, 22 eyes with retinal vascular disease, and 7 normal eyes (cohort A). The subgroup of eyes with

suboptimal OCTA scans included 21 eyes that had one or both OCTA scans with signal strength < 6 (cohort B). The clinical features of these two subgroups were similar. The mean values ± standard errors of the OCTA signal strengths for cohort A were 7.85 ± 0.86 and 7.68 ± 0.76 for the right and left eyes, respectively. The mean values ± standard error for the scans of cohort B were 5.17 ± 1.89 and 5.60 ± 1.96 for right and left eyes, respectively.

Table 2 summarizes the ICC values for RPC density of each OCTA region for the total cohort, as well as cohorts A and B. For the total cohort, the calculated ICC values demonstrate excellent repeatability of RPC density for all OCTA regions analyzed except for inside the disc and the temporal quadrant, both of which demonstrated good repeatability. For cohort A, the repeatability was excellent with ICC values that were slightly higher for each OCTA region analyzed when compared to the total cohort. The ICC values were 0.962 (95% confidence interval (CI) = 0.925 – 0.981) for the whole image and 0.971 (95% CI = 0.943 – 0.986) for the peripapillary region. For cohort B, the repeatability of the superior quadrant was excellent, but all other zones had ICC values that correspond to moderate to good repeatability. For the whole image and peripapillary zone, the ICC was significantly lower in cohort B when compared to cohort A based on the 95% confidence intervals.

Table 2 also gives the ICC values for the subset of eyes with optic atrophy, the subset of eyes with disc edema from low-grade papilledema, and the subset of eyes with retinal vascular disease. For these subsets, ICC values were calculated for the RPC density measurement of the whole image and that of the peripapillary region. Both eyes with optic atrophy and eyes with papilledema demonstrated excellent repeatability for both the peripapillary region (ICC = 0.980 (95% CI = 0.904 – 0.996) and 0.966 (95% CI = 0.854 – 0.993), respectively) and the whole disc (ICC = 0.954 (95% CI = 0.804 – 0.990) and 0.921 (95% CI = 0.711 – 0.982), respectively). Repeatability for RPC density measurement for the subset of eyes with retinal vascular disease was also excellent for the peripapillary region (ICC = 0.916 (95% CI = 0.827 – 0.961)) and good for the whole image (ICC = 0.895 (95% CI = 0.788 – 0.951)).

## Conclusions

In this study, we used the latest version of a commercially available OCTA software to quantitate the peripapillary capillary density in eyes with optic neuropathy and retinal vasculopathy and to assess repeatability of these measurements. The Optovue AngioVue was used since it is the only commercially available OCTA device to date with FDA-approved software that automatically quantitates the peripapillary capillary density (i.e. RPC density) for various regions around the disc.

Evaluating the repeatability of OCTA quantitative parameters is important since various factors can affect repeatability of these parameters including instruments being used, image quality, and presence of retinal or optic nerve pathology.[14–21] Lei et al. used four different OCTA instruments and showed that all four instruments have good to excellent repeatability of the vascular length measurement of the peripapillary capillary network using the same instrument.[19] However, the study was limited to normal eyes and the measurements were significantly different among machines made by different vendors. Similar differences in measurement of other quantitative OCTA parameters such as retinal vascular density

and foveal avascular zone, have been noted using OCTA machines made by different vendors.[19–20]

Therefore, our study limited the peripapillary capillary density repeatability analysis to one OCTA device, Optovue AngioVue, and used the latest software available. This OCTA device has been shown to yield highly repeatable quantitative OCTA parameters including retinal vascular density and foveal avascular zone size measurement in normal eyes and eyes with retinopathy.[19, 21] Furthermore, quantitation of peripapillary capillary density, i.e. RPC density, was noted to be highly repeatable in normal eyes and eyes with glaucoma using this device.[14–16]

We found excellent repeatability (ICC > 0.9) for RPC density measurement for our total cohort for all OCTA zones analyzed except inside the disc and the temporal peripapillary quadrant, both of which demonstrated good repeatability (ICC = 0.885 (95% CI = 0.805 – 0.935) and 0.851 (95% CI = 0.756 – 0.913), respectively). When analyzing only the subset of eyes with good OCTA image quality (i.e. signal strength ≥ 6), ICC improved slightly for all examined regions to ≥ 0.9 but the difference was not significant based on the 95% confidence intervals. Conversely, for the subset of eyes with poor OCTA image quality (i.e. signal strength <6), the ICC was good to moderate and significantly lower than cohort A only for 2 zones. In other words, OCTA repeatability can be affected by suboptimal image quality but only moderately.

Our study also demonstrated good to excellent repeatability of RPC density measurements of the subset of eyes with optic nerve or retinal vascular disease. Among eyes with optic atrophy or optic disc edema from papilledema, RPC density repeatability was excellent for the whole disc and peripapillary zone. Similarly, in eyes with retinal vasculopathy, RPC density repeatability was good for the whole image and excellent for the peripapillary region. To our knowledge, this is the first study evaluating repeatability of RPC density measurement using a commercial OCTA in eyes with optic atrophy, optic disc edema, or retinal vasculopathy.

Our study has several limitations. Firstly, we had a relatively small sample size especially for the subset analysis. Secondly, all eyes with disc edema had low grade papilledema in our study. Thus, our study findings may not be applicable to eyes with more severe disc edema or disc edema from causes other than papilledema. Of note, one eye excluded from our study for poor centration of the OCTA image had grade 3 disc edema. It is possible that anatomic changes in the disc with severe disc edema may result in suboptimal centration and segmentation of the OCTA image. Eyes with more severe papilledema were noted previously to have lower RPC.[12] Lastly, our study was limited to one commercial OCTA instrument. Thus, the findings may not be generalizable to other OCTA devices or other versions of the Optovue device.

In summary, our study found high repeatability of RPC density measurements using OCTA in normal eyes and eyes with optic atrophy, low-grade disc edema from papilledema or retinal vasculopathy. The high repeatability was only moderately affected by image quality. These findings support the hypothesis that RPC density measurement obtained using this

latest version of OCTA software is a reliable and repeatable quantitative parameter. Future research is needed to determine if RPC density measurement obtained using OCTA is a useful biomarker for diagnosis and management of optic nerve and retinal vascular diseases.

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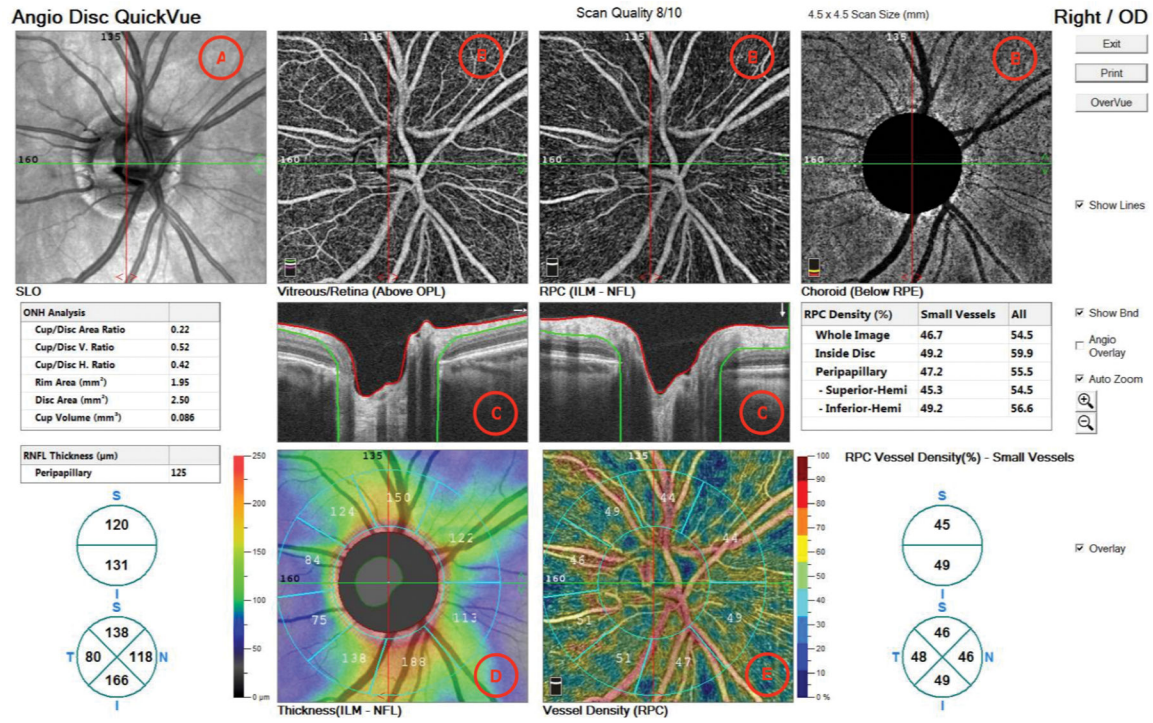


**Figure 1:**

Representative view of Optovue RTVue data interface. An en-face infrared image of the optic disc (A) is displayed to the left of corresponding OCT angiographic images of different layers (B). Vertical and horizontal OCT B-scans (C) are displayed centrally. On the left side, automated measurements of the thickness of the retinal nerve fiber layer (RNFL) are displayed numerically (as a whole and by sectors) as well as graphically with a heat map (D). On the right side, the radial peripapillary capillary (RPC) density is portrayed in a similar fashion (E).

**Table 1:**

Patient Demographics and Clinical Features: Comparing cohort A with good image quality OCTA scans with cohort B with suboptimal quality OCTA scans[1]

| | Total Cohort | Cohort A | Cohort B | p-value[2] |
|---|---|---|---|---|
| **Number of Patients** | 31 Patients | 26 Patients | 13 Patients | |
| **Number of Eyes** | 59 Eyes (29 OD) | 40 Eyes (20 OD) | 19 Eyes (9 OD) | |
| **Age** | 56 ± 3.3 | 68 ± 1.4 | 53 ± 5.2 | p = 0.23288 |
| **Gender** | 13M (42%), 18F | 10M (40%), 15F | 3M (50%), 3F | |
| **Diabetes Mellitus Type 1** | 2 (6%) | 2 (8%) | 0 (0%) | |
| **Diabetes Mellitus Type 2** | 14 (45%) | 9 (36%) | 5 (80%) | |
| **Hypertension** | 20 (65%) | 16 (64%) | 4 (60%) | |
| **Hyperlipidemia** | 21 (68%) | 16 (64%) | 5 (80%) | |
| **Optic Atrophy** | 7 (12%) | 4 (10%) | 3 (14%) | p = 0.70605 |
| **CNS Mass** | 4 (7%) | 2 (5%) | 2 (10%) | |
| **AION** | 2 (3%) | 1 (3%) | 1 (5%) | |
| **Resolved Papilledema** | 1 (2%) | 1 (3%) | 0 (0%) | |
| **Disc edema from Papilledema** | 9 (15%) | 7 (18%) | 2 (10%) | p = 0.64630 |
| **Grade ≤1** | 7 (12%) | 6 (15%) | 1 (5%) | |
| **Grade 2** | 2 (6%) | 1 (3%) | 1 (5%) | |
| **Vascular Retinopathy** | 35 (59%) | 22 (55%) | 13 (62%) | |
| **RVO** | 6 (10%) | 5 (13%) | 1 (5%) | |
| **NPDR** | 13 (22%) | 7 (18%) | 6 (29%) | |
| **PDR** | 11 (19%) | 8 (20%) | 3 (14%) | |
| **Normal** | 8 (14%) | 7 (18%) | 1 (5%) | p = 0.32284 |
| **BCVA OD (LogMAR)** | 0.23 ± 0.03 | 0.22 ± 0.04 | 0.26 ± 0.06 | p = 0.65546 |
| **BCVA OS (LogMAR)** | 0.33 ± 0.07 | 0.22 ± 0.06 | 0.51 ± 0.13 | p = 0.23288 |
| **Phakic Status OD** | 21/29 (72%) | 15/20 (75%) | 6/9 (67%) | |
| **Phakic Status OS** | 23/31 (74%) | 15/10 (75%) | 8/10 (80%) | |
| **RNFL Thickness OD** | 106.3 ± 5.9 | 105.6 ± 11.2 | 106.7 ± 8.2 | p = 0.93175 |
| **RNFL Thickness OS** | 107.2 ± 7.7 | 91.8 ± 6.6 | 114.9 ± 14.5 | p = 0.32284 |

[1]Abbreviations: CNS, central nervous system; AION, anterior ischemic optic neuropathy; RVO, retinal vein occlusion; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; BCVA, best-corrected visual acuity; OD, right eye; OS, left eye; RNFL, retinal nerve fiber layer. ± values represent standard errors of the mean.

[2]P-values were calculated to compare cohort A versus cohort B. A two-tailed Student's t-test was used to compare means and a Chi-squared test was used to compare proportions. A p-value of <0.05 was considered statistically significant.

**Table 2:**

Repeatability of RPC Vessel Density Measurement of Optic Disc using OCTA

| | ICC | 95% Confidence Interval |
|---|---|---|
| **Total Cohort** | | |
| Whole Image | 0.915 | 0.855 – 0.951 |
| Inside Disc | 0.885 | 0.805 – 0.935 |
| Peripapillary | 0.945 | 0.905 – 0.969 |
| Superior Quadrant | 0.948 | 0.913 – 0.969 |
| Nasal Quadrant | 0.920 | 0.863 – 0.954 |
| Inferior Quadrant | 0.936 | 0.891 – 0.964 |
| Temporal Quadrant | 0.851 | 0.756 – 0.913 |
| **Cohort A** | | |
| Whole Image | 0.962 | 0.925 – 0.981 |
| Inside Disc | 0.904 | 0.822 – 0.951 |
| Peripapillary | 0.971 | 0.943 – 0.986 |
| Superior Quadrant | 0.957 | 0.917 – 0.978 |
| Nasal Quadrant | 0.949 | 0.900 – 0.974 |
| Inferior Quadrant | 0.962 | 0.924 – 0.981 |
| Temporal Quadrant | 0.926 | 0.858 – 0.963 |
| **Cohort B** | | |
| Whole Image | 0.710 | 0.445 – 0.882 |
| Inside Disc | 0.814 | 0.592 – 0.929 |
| Peripapillary | 0.843 | 0.659 – 0.937 |
| Superior Quadrant | 0.922 | 0.820 – 0.968 |
| Nasal Quadrant | 0.862 | 0.681 – 0.948 |
| Inferior Quadrant | 0.857 | 0.691 – 0.942 |
| Temporal Quadrant | 0.679 | 0.383 – 0.878 |
| **Eyes with Optic Atrophy** | | |
| Whole Image | 0.954 | 0.804 – 0.990 |
| Peripapillary | 0.980 | 0.904 – 0.996 |
| **Eyes with Papilledema** | | |
| Whole Image | 0.921 | 0.711 – 0.982 |
| Peripapillary | 0.966 | 0.854 – 0.993 |
| **Eyes with Retinal Vasculopathy** | | |
| Whole Image | 0.895 | 0.788 – 0.951 |
| Peripapillary | 0.916 | 0.827 – 0.961 |