Title

Diurnal Variations of Peripapillary and Macular Vessel Density in Glaucomatous Eyes Using Optical Coherence Tomography Angiography

Journal

Journal of Glaucoma, 27(4)

ISSN

1057-0829

Authors

Mansouri, Kaweh
Rao, Harsha L
Hoskens, Kirsten
et al.

Publication Date

2018-04-01

DOI

10.1097/ijg.0000000000000914

Peer reviewed

HHS Public Access

Author manuscript

J Glaucoma. Author manuscript; available in PMC 2023 May 17.

Published in final edited form as:

J Glaucoma. 2018 April ; 27(4): 336–341. doi:10.1097/IJG.0000000000000914.

Diurnal Variations of Peripapillary and Macular Vessel Density in Glaucomatous Eyes Using Ocular Coherence Tomography Angiography

Kaweh Mansouri, M.D., M.P.H.[1,2], **Harsha L Rao**[4], **Kirsten Hoskens, M.D.**[1], **Elisa D'Alessandro, M.D.**[1], **Elsa M. Flores-Reyes, M.D.**[1,5], **André Mermoud, M.D.**[1], **Robert N Weinreb, M.D.**[3]

[1]Glaucoma Research Center, Montchoisi Clinic, Swiss Vision Network, Lausanne, Switzerland.

[2]Department of Ophthalmology, University of Colorado School of Medicine, Denver, CO, USA.

[3]Hamilton Glaucoma Center and Shiley Eye Institute, Department of Ophthalmology, University of California, San Diego, CA, USA.

[4]Narayana Nethralaya, Rajajinagar, Bangalore, India.

[5]Department of Glaucoma, Instituto de Oftamologia "Conde de Valenciana", Mexico City, Mexico.

Abstract

Purpose: To investigate the diurnal variation in peripapillary and macular vessel density (VD) measurements using optical coherence tomography angiography (OCT-A) and its correlation to intraocular pressure (IOP) changes in glaucoma patients.

Methods: Prospective, observational cross-sectional study including 37 patients (74 eyes; age, 63.8±12.9 years) with open angle glaucoma. OCT-A imaging and IOP measurements were performed at 08:00, 11:00, 14:00, and 16:00 on a single day. At each time-point, two scan protocols were used to generate 3-dimensional en-face OCT angiograms: 4.5 × 4.5-mm scan centered on optic nerve head and 6 × 6-mm scan centered on the fovea. For each scan mode, the "Radial Peripapillary Capillary (RPC)" segment, composed of the vasculature of the RNFL and ganglion cell layer, was calculated. Two trained readers reviewed OCT-A image quality. Only scans with signal strength intensity (SSI) higher than 46 and without image artifacts interfering with measurements were included. Variation in VD measurements assessed using analysis of variance (ANOVA) and the association between VD and IOP changes assessed using linear mixed modeling methods.

Results: The ONH and peripapillary VD measurements at 14:00 and 16:00 time points were greater than the measurements at 08:00 and 11:00 time points. The 14:00 and 16:00 VD measurements were statistically significantly greater ($p<0.05$) than the 08:00 measurements for

Corresponding author: Kaweh Mansouri, MD MPH, Glaucoma Research Center, Montchoisi Clinic, Swiss Vision Network, Lausanne, Switzerland. Phone: +41 (21) 619-37-42. Fax: +41 (21) 619-36-28. kwmansouri@gmail.com.

Financial Disclosures: Mansouri K: Santen (C), Sensimed (C), Topcon (S), Alcon (S), Allergan (S), Optovue (S); Rao HL: Pfizer (C), Santen (C), Cipla (C); Hoskens K: none; D'Alessandro E: none; Flores-Reyes EM: none; Mermoud A: Alcon (S), Allergan (S), Weinreb RN: Optovue (S), Topcon (S), Meditec-Zeiss (S), Heidelberg Engineering (S), Genentech (S), Allergan (C), Alcon (C), Eyenovia (C), Bausch & Lomb (C), Sensimed (C), Unity (C)

the whole enface (50.1% and 50.1% vs 49.4%), inside disc (50.6% and 50.5% vs 49.6%) and average peripapillary (58.2% and 58.5% vs 57.5%) VDs. The macular VD measurements at the 14:00 time point were greater than the measurements at 08:00and 11:00 time points. Changes in VD were significantly associated with changes in SSI but not IOP.

Conclusions: Diurnal changes in OCT-A measured VD in glaucoma patients were small and clinically insignificant. These changes were not associated with IOP changes.

Glaucoma is characterized by progressive retinal nerve fiber loss and a concomitant pattern of visual field damage. The pathogenesis of glaucomatous optic neuropathy is still poorly understood.(1) Two principal theories, a mechanical and a vascular theory, have been described. The mechanical theory considers increased intraocular pressure (IOP) to be the cause of retinal ganglion cell axonal injury, and IOP reduction still remains the mainstay of glaucoma treatment. However, in some patients lowering of IOP is insufficient to stop disease progression.(1) In contrast to the mechanical theory, the vascular theory considers insufficient blood supply to be the cause of glaucomatous optic neuropathy. Several studies have suggested that vascular factors play an important role in the pathogenesis of glaucoma. (2, 3)

Different methods have been to assess ocular blood flow. Fluorescein angiography requires the injection of fluorescent dye and can be used, to some extent, to evaluate the superficial retinal circulation and the optic nerve head circulation. Color Doppler imaging is an ultrasound technique that can be used to assess the blood flow velocity of retrobulbar vessels.(4, 5) Results can be obtained from blood flow in the larger vessels like the ophthalmic artery, but measurements of other vessels, even as large as individual short posterior ciliary arteries remain difficult. Furthermore, reproducibility of measurements is low, since it is a subjective and user-dependent technique.(6)

The recent introduction of optical coherence tomographic angiography (OCT-A) has allowed for the noninvasive and depth-resolved imaging of the retinal and peripapillary microvasculature without the injection of exogenous dyes.(7) OCT-A provides volumetric blood flow information using motion contrast generated by erythrocyte movement. Multiple approaches for OCT-A have been developed. One such method uses an algorithm to calculate blood flow, termed split-spectrum amplitude-decorrelation angiography (SSADA). The SSADA algorithm calculates the decorrelation in reflected light from moving red blood cells at consecutive points, allowing the vasculature to be visualized.(8) OCT-A allows visualization of the radial peripapillary capillaries (RPC) that supply the retinal nerve fiber layer (RNFL). This vascular network could not be visualized previously with traditional technologies. Previous studies have demonstrated that OCT-A can quantify vessel density (VD) of the optic nerve head in glaucoma patients.(9, 10)

IOP is a dynamic biological parameter with an individual circadian rhythm.(11) Other risk factors associated with the vascular etiology of glaucoma, such as systemic blood pressure, ocular perfusion pressure and ocular blood flow have also been demonstrated to follow circadian patterns. However, various techniques have been used to evaluate circadian ocular blood flow fluctuations in glaucoma patients, and there have been contradictory results.(5, 12, 13) For instance, studies in choroidal thickness have revealed thicker choroid in the

morning than in the evening and after water loading.(14, 15) At present, there are no available data on diurnal variations of OCT-A parameters. It is, however, indispensable to know the normal variation of a parameter and its associations with other biological variables if the new parameter is to be used for diagnostic purposes.

The purpose of the current study is to evaluate diurnal fluctuations in optic nerve head and macular vessel density as measured by OCT-A in glaucoma patients. We further aim to evaluate the correlation between diurnal vessel density and IOP variations.

METHODS

This was a prospective, observational, cross-sectional study performed at the Glaucoma Research Center, Montchoisi Clinic, Swiss Vision Network, Lausanne after approval by the institutional review board. Written consent was obtained from each patient. The study adhered to the tenets of the Declaration of Helsinki and was registered at ClinicalTrials.gov (identifier, NCT02757677).

Study Population

Patients with open angle glaucoma (OAG) were prospectively enrolled between December 2015 and May 2016. Eligible patients were aged 18 years or older with a diagnosis of primary or secondary open angle glaucoma (OAG). Eyes were classified as glaucomatous if they had repeatable (2 consecutive) abnormal standard automated perimetry test results (Octopus, Haag Streit, Koeniz, Switzerland) in the presence of abnormal-appearing optic discs (presence of neuroretinal rim thinning or localized or diffuse RNFL defects indicative of glaucoma) by slit lamp assessment or SD-OCT. Visual field exams required reliability indices better than 15%. Gonioscopy was performed on all eyes prior to study inclusion. Open angles were a requirement for study inclusion. Patients with a history of intraocular surgery (except for uncomplicated cataract surgery), coexistent retinal pathologies and other ocular pathologies were excluded from the study. Both eyes of each patient had to be eligible and were enrolled in the study. Patients were selected from the investigators' glaucoma clinics. For all patients, the following data were recorded: age, gender, diagnosis, best-corrected visual acuity, IOP with Goldmann applanation tonometry, central corneal thickness, mean RNFL thickness (Spectralis OCT, Heidelberg Engineering AG, Germany), and visual field mean deviation (MD) and square of loss variance (sLV). IOP measurements were performed using Goldmann applanation tonometry at 8:00, 11:00, 14:00, and 16:00 on a single day. The patients had been advised to refrain from coffee consumption and physical exercise during the study day.

OCT-A Image Acquisition and Processing

The commercially available Avanti SD-OCT device (RTVueXR Avanti; Optovue Inc, Fremont, CA, USA) with AngioVue software was used for imaging. This system uses an 840 nm superluminescent diode with a bandwidth of 45 nm, operated at 70,000 A-scans per second. The SSADA software algorithm (version 2016.1.0.26) was used to capture the dynamic motion of erythrocytes and create a high-resolution three-dimensional visualization

of perfused retinal vasculature. The technique of OCT-A with SSADA has been described in detail elsewhere.(8–10, 16)

OCT-A scans were acquired by trained and experienced technicians. Scans were obtained through undilated pupils whenever possible. At each time-point, 4 scan protocols were acquired to generate 3-dimensional en-face OCT angiograms: 3 × 3-mm and 4.5 × 4.5-mm scan centered on optic nerve head (ONH) using the Angio Disc mode, 6 × 6-mm scan centered on the fovea, and 6 × 6-mm scan centered on the area between the macula and the ONH using the Angio Retina mode. The AngioVue provides vascular information at various retinal layers selected by the user, which are provided as a vascular density map and quantitatively as vascular density (%). Vascular density was calculated as the percentage area occupied by blood vessels, with the blood vessels being defined as pixels having decorrelation values above the threshold level.

The AngioAnalytics software (v2016.1.0.26) was used for automated quantification of vascular density measurements. Herein, vascular density is calculated by first extracting a binary image of the vessels from the OCT-A en face image, and then computing the percentage of voxels in defined sectors based on the binary image. For macula scans, the vascular density was provided in the sectors (superior, temporal, inferior, and nasal) based on the Early Treatment Diabetic Retinopathy Study (EDTRS) chart. For optic disc scans, vascular density (VD) was provided for the whole enface image (wiVD), for the circumpapillary region (cpVD) defined as a 750-μm-wide elliptical annulus extending from the optic disc boundary, and for each of the six sectors of the cpVD. For each scan mode, the “Radial Peripapillary Capillary (RPC)” segment was calculated. The “RPC” reference corresponds to the superficial capillary plexus composed of the vasculature of the RNFL and ganglion cell layer. The peripapillary region was divided into 6 sectors based on the Garway-Heath map and the vessel density in each sector was calculated (nasal, inferonasal, inferotemporal, superotemporal, superonasal and temporal sectors).(17). Data were exported from the OCT-A device as electronic csv. files.

Two trained and independent readers (E. D., E. F. R.) reviewed all images. Patients with poor image quality were excluded based on the standard protocol established by the University of California, San Diego Imaging Data Evaluation and Analysis (IDEA) Reading Center. (18) In brief, images were excluded based on 1 or more of the following criteria: 1) low signal strength index (SSI; less than 46), 2) poor clarity obscuring view of the vasculature, 3) motion artifacts visible as irregular vessel patterns, or 4) RNFL segmentation errors. The location of disc margin was reviewed for accuracy and adjusted manually whenever required.

Statistical Analysis

Quantitative data were described by their mean and standard deviation (SD). The distribution of numerical data was tested for normality using the Shapiro-Wilk test. Effect of IOP and SSI values on the diurnal changes of vessel density measurements was evaluated using linear mixed effects models for repeated measures. Linear mixed model is a parametric linear model which quantifies the relationship between a continuous dependent variable and one or more independent (determinant) variables, specifically used

with clustered, longitudinal or repeated measures data.(19) It can include fixed and random effect-parameters, accounting for the correlation among random effect-parameters. While the fixed effect-parameters describe the relationship between the independent and the dependent variable for the entire cohort, random effect-parameters, in the context of our study, describe the relationship specifically between the repeated measurements of vessel density and SSI and IOP values within each subject of the cohort. Analysis of variance (ANOVA) models were used to compare VD measurements of the ONH, peripapillary and macular regions at various time points of the day to evaluate the significance of the diurnal changes in VD measurements.

All tests were two-tailed and a *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed with commercially available software (Stata version 13.1; StataCorp, College Station, TX).

RESULTS

A total of 86 eyes of 43 glaucoma patients were included in the study. Data from 6 patients were excluded from the analysis: In 5 patients, image quality was insufficient at all time points and 1 patient was unable to complete measurements at all 4 time points. Therefore, the study analysis included 74 eyes of 37 patients (age, 63.8 ± 12.9 years; range, 20–90). All patients were of Caucasian origin. In all, 4 patients had no treatment after previous successful selective laser trabeculoplasty, 26 patients were on monotherapy with prostaglandin analogues (PGA), 5 patients were on dual therapy with PGA and topical carbonic anhydrase inhibitors, and 2 patients were on a PGA+beta-blocker combination therapy. Patient characteristics are listed in Table 1.

Mean IOP was 16.3 ± 4.2, 16.4 ± 4.5, 16.2 ± 4.1 and 15.9 ± 4.3 mmHg at 08:00, 11:00, 14:00 and 16:00 respectively. Mean SSI was 63.5 ± 8.5, 64.8 ± 9.0, 64.2 ± 10.1 and 64.3 ± 8.6 at 08:00, 11:00, 14:00 and 16:00 for the optic disc scans and 60.1 ± 8.4, 60.3 ± 8.8, 60.6 ± 8.9 and 59.7 ± 8.7 for the macula scans. The results of the repeated measures mixed-effects models evaluating the association between diurnal changes in VDs and changes in IOP and SSI are shown in Table 2a and 2b. Changes in IOP were not significantly associated with diurnal changes in the VD measurements either in the peripapillary or the macular regions. However, changes in SSI were significantly associated with changes in VD measurements both in peripapillary and macular regions. VDs increased with increase in SSIs of the repeat scans. The increase in VDs with increase in SSI values of repeat scans were greater in the macula compared to the ONH and peripapillary regions. The diurnal changes in VDs were therefore evaluated after accounting for the effect of change in SSI values of the repeat scans.

The SSI-adjusted diurnal VD measurements are shown in Tables 3a–3b. The ONH and peripapillary VD measurements at 14:00 and 16:00 time points were greater than the measurements at 8:00 and 11:00 time points. However, the afternoon measurements (14:00 and 16:00) were statistically significantly greater than the morning measurements (08:00) only for the whole enface, inside disc, average peripapillary and nasal sector peripapillary VDs. The macular VD measurements at the 14:00 time point were greater than the

measurements at 08:00 and 11:00 time points. However, the 14:00 time point measurement was statistically significantly greater than the 08:00 and 16:00 measurements only in the nasal parafoveal sector.

We ran the whole analysis considering one eye randomly from patients who contributed both eyes for the initial analysis and found similar results. Changes in IOP were not associated ($p>0.05$ for all associations) with diurnal changes in the VD measurements either in the peripapillary (coefficients ranging from −0.20 to 0.25) or the macular (coefficients ranging from 0.10 to 0.19) regions. And, changes in SSI were significantly associated ($p<0.05$ for all associations) with changes in VD measurements both in peripapillary (coefficients ranging from 0.15 to 0.30) and macular regions (coefficients ranging from 0.40 to 0.54). There were no statistically significant differences ($p>0.05$ for all associations) in the VD measurements at the four time points either in the peripapillary or the macular region.

Tables 4 presents the repeatability estimates of peripapillary and macular vessel density measurements.

DISCUSSION

Our results show that diurnal IOP fluctuations that were within what is generally considered to be physiological range were not significantly associated with diurnal changes in the VD measurements. ONH and peripapillary VD measurements at the 14:00 and 16:00 time points were significantly greater than the measurements at the 08:00 and 11:00 time points. Macular VD measurements at the 14:00 time point were also greater than the measurements at 08:00 and 11:00 time points. These diurnal differences, however, were relatively small and within the test-retest variability reported by previous studies.(20)

Previous studies have evaluated the repeatability of OCT-A measured vessel densities in the peripapillary and the macular regions. (9, 20–22) However, the repeatability estimates in most of these studies were performed predominantly in normal subjects and on small samples. Also, most of the studies only calculated the average vessel density and did not report results by sectors. Liu et al.,(9) investigated the average peripapillary VD in 12 normal and 12 glaucoma eyes and found a coefficient of variation (CV) of 1.9% and 4% respectively. Similar results of peripapillary VD repeatability were found by Wang et al.,(22) who reported a CV of 1.2% in 15 normal eyes. Hollo, (21) evaluated intra- and inter-session repeatability of peripapillary VD measurements in 18 glaucoma eyes. This sample was obtained out of a total of 83 eyes, wherein image quality of 65 eyes was insufficient for analysis. Intra-session CV ranged between 2.30 and 3.89%, while the inter-session CV values ranged between 3.05 and 4.26%. Therefore, intra-session variability seemed to explain most of the inter-session variability.

Whether OCT-A has a role in the clinical care of glaucoma patients remains unclear. Liu et al.,(9) evaluated peripapillary retinal perfusion in 12 glaucoma eyes and compared it with 12 age-matched healthy eyes. They showed a dense microvascular capillary network around the ONH in healthy eyes, which was significantly attenuated in the glaucoma eyes. Using the OCT-A’s vascular density parameter, the discriminating ability between glaucoma

vs. normal eyes (area under ROC curve) was a strong 0.938. Interestingly, the authors found a strong correspondence (Pearson r = −0.835) between functional loss in glaucoma eyes (assessed by perimetry) and structural damage to the optic nerve. Leveque et al.,(23) and Yarmohammadi et al.,(18) demonstrated that there is a decrease in vascular density in glaucoma patients compared to healthy controls. A relationship between glaucoma severity and decrease in vascular density has also been shown.(18) Furthermore, both studies showed that structural loss, such as RNFL thickness, was correlated with decreases in vascular density. The spatial correlation of RNFL thinning and losses of the RPC were also shown by Hollo (24).

The ability to reliably detect progressive changes in vessel density would be an essential feature for OCT-A technology in glaucoma imaging. Recently, Venugopal et al., (20) compared the intra-session repeatability of peripapillary and macular VD measurements in 65 normal and glaucoma eyes. They obtained 3 consecutive optic nerve head and macular scans within the same session and found similar measures of repeatability in both groups. CV ranged between 2.5% and 4.4% in normal and 2.6% and 6.6% in glaucoma eyes. For the macula, these ranged between 3.3% and 4.7%, and 3.7% and 5.6%, respectively. One notable difference was found in measurements of the inferotemporal sector of the optic nerve head, where the repeatability was significantly worse in the glaucoma eyes. This was an interesting finding as this sector is the one most often affected in the glaucomatous disease progress. It is, therefore, likely that VD measurements would become less repeatable with increased glaucomatous damage. Repeatability estimates were lower in our study with a CV of 3.7 and 5.7 for the peripapillary and macular Whole en face parameters, respectively (vs. 2.6 and 3.7 in Venugopal et al.(20)). This difference is likely explained by the 4 diurnal readings in our study (vs. 3 in Venugopal et al.)(20). Hollo,(21) also reported that VD repeatability varied across the various peripapillary sectors. Similar to the study by Venugopal et al.,(20) the disease severity was mild in most of the patients in our study (average MD −4.7 dB vs −4.9 dB in our study).

We found that changes in SSI were the only factor significantly associated with changes in VD. With increasing SSI, there was an increase in both peripapillary and macular VD measurements. Venugopal et al.,(20) also reported a significant positive association of between the two variables, with coefficients ranging from 0.15 to 0.38. These results point to the importance of obtaining high quality OCT-A images and adjusting for SSI when interpreting changes in VD over time.

There are several limitations to our study. Some limitations are related to OCT-A technology. OCT-A with SSADA has a resolution of 18 μm, rather than the 5 μm for a full bandwidth algorithm.(25) Therefore, smaller vascular changes may have remained undetected. In this study, eyes were not dilated systematically. It is possible that image quality would have improved and resulted in higher reproducibility of VD measurements if the pupils were dilated. Finally, our results were obtained with the RTVue device and may not apply to other OCT-A technologies. Other limitations include the absence of diurnal blood pressure measurements during. Eight patients were known to suffer from high blood pressure, all of which were on systemic antihypertensive medications. Furthermore, it is possible that anti-glaucoma medications influence the diurnal change in vessel density

measurements. Although there are no studies in the literature evaluating the effect of anti-glaucoma medications on OCT-A measurements, a previous meta-analysis has reported increased ocular blood flow with topical carbonic anhydrase inhibitors.(26) Therefore, anti-glaucoma medications could have influenced the diurnal changes in VD measurements seen in our study. However, our study sample of patients on topical carbonic anhydrase inhibitors was too small to allow us to perform a subgroup analysis. Future research should evaluate diurnal VD changes in untreated glaucoma patients and in sub-groups of treated glaucoma patients. The absence of a control group of healthy subjects is a limitation of this study. However, due to the absence of a statistically significant diurnal variation of OCT-A measurements (with the exception of the 14:00 measurement) and absence of a correlation to IOP changes, we do not believe that the inclusion of a control group would have affected the findings of this study. Furthermore, despite the general understanding that IOP fluctuations are higher in glaucoma patients than healthy subjects, it is conceivable that some healthy subjects would have presented higher IOP fluctuations during the day than our tightly controlled glaucoma patients.(11)

In conclusion, diurnal IOP variations did not have a significant effect on OCT-A measured peripapillary and macular vessel densities in glaucomatous eyes. Overall, OCT-A measurements were similar when repeated several times on a single day. Image quality (SSI values) had a significant effect on the OCT-A measurements and should be considered when interpreting longitudinal changes of vessel density measurements.

Funding/Support:

Supported in part by the Swiss Glaucoma Research Foundation, Lausanne, Switzerland.

REFERENCES:

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–11. [PubMed: 24825645]
2. Flammer J, Orgul S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, et al. The impact of ocular blood flow in glaucoma. Progress in retinal and eye research. 2002;21(4):359–93. [PubMed: 12150988]
3. Flammer J, Mozaffarieh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? Surv Ophthalmol. 2007;52 Suppl 2:S162–73. [PubMed: 17998042]
4. Martinez A, Sanchez M. Predictive value of colour Doppler imaging in a prospective study of visual field progression in primary open-angle glaucoma. Acta ophthalmologica Scandinavica. 2005;83(6):716–22. [PubMed: 16396650]
5. Stalmans I, Vandewalle E, Anderson DR, Costa VP, Frenkel RE, Garhofer G, et al. Use of colour Doppler imaging in ocular blood flow research. Acta Ophthalmol. 2011;89(8):e609–30. [PubMed: 21989301]
6. Plange N, Kaup M, Weber A, Harris A, Arend KO, Remky A. Performance of colour Doppler imaging discriminating normal tension glaucoma from healthy eyes. Eye. 2009;23(1):164–70. [PubMed: 17693998]
7. Mansouri K Optical coherence tomography angiography and glaucoma: searching for the missing link. Expert review of medical devices. 2016:1–2.
8. Jia Y, Tan O, Tokayer J, Potsaid B, Wang Y, Liu JJ, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Optics express. 2012;20(4):4710–25. [PubMed: 22418228]

9. Liu L, Jia Y, Takusagawa HL, Pechauer AD, Edmunds B, Lombardi L, et al. Optical Coherence Tomography Angiography of the Peripapillary Retina in Glaucoma. JAMA ophthalmology. 2015;133(9):1045–52. [PubMed: 26203793]
10. Pechauer AD, Jia Y, Liu L, Gao SS, Jiang C, Huang D. Optical Coherence Tomography Angiography of Peripapillary Retinal Blood Flow Response to Hyperoxia. Investigative ophthalmology & visual science. 2015;56(5):3287–91. [PubMed: 26024111]
11. Aptel F, Weinreb RN, Chiquet C, Mansouri K. 24-h monitoring devices and nyctohemeral rhythms of intraocular pressure. Progress in retinal and eye research. 2016.
12. Okuno T, Sugiyama T, Kojima S, Nakajima M, Ikeda T. Diurnal variation in microcirculation of ocular fundus and visual field change in normal-tension glaucoma. Eye. 2004;18(7):697–702. [PubMed: 14739923]
13. Pemp B, Georgopoulos M, Vass C, Fuchsjager-Mayrl G, Luksch A, Rainer G, et al. Diurnal fluctuation of ocular blood flow parameters in patients with primary open-angle glaucoma and healthy subjects. The British journal of ophthalmology. 2009;93(4):486–91. [PubMed: 19029154]
14. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. Investigative ophthalmology & visual science. 2012;53(1):261–6. [PubMed: 22167095]
15. Mansouri K, Medeiros FA, Marchase N, Tatham AJ, Auerbach D, Weinreb RN. Assessment of choroidal thickness and volume during the water drinking test by swept-source optical coherence tomography. Ophthalmology. 2013;120(12):2508–16. [PubMed: 24021895]
16. Jia Y, Wei E, Wang X, Zhang X, Morrison JC, Parikh M, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. Ophthalmology. 2014;121(7):1322–32. [PubMed: 24629312]
17. Garway-Heath DF, Poinoosawmy D, Fitzke FW, Hitchings RA. Mapping the visual field to the optic disc in normal tension glaucoma eyes. Ophthalmology. 2000;107(10):1809–15. [PubMed: 11013178]
18. Yarmohammadi A, Zangwill LM, Diniz-Filho A, Suh MH, Manalastas PI, Fatehee N, et al. Optical Coherence Tomography Angiography Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes. Investigative ophthalmology & visual science. 2016;57(9):OCT451–9. [PubMed: 27409505]
19. West BT, Welch KB, Galecki AT. Linear mixed models: a practical guide using statistical software. Boca Raton: CRC Press; 2007.
20. Venugopal JP, Rao HL, Weinreb RN, Pradhan ZS, Dasari S, Riyazuddin M, et al. Repeatability of vessel density measurements of optical coherence tomography angiography in normal and glaucoma eyes. The British journal of ophthalmology. 2017.
21. Intrasession Hollo G. and Between-Visit Variability of Sector Peripapillary Angioflow Vessel Density Values Measured with the Angiovue Optical Coherence Tomograph in Different Retinal Layers in Ocular Hypertension and Glaucoma. PloS one. 2016;11(8):e0161631. [PubMed: 27537500]
22. Wang X, Kong X, Jiang C, Li M, Yu J, Sun X. Is the peripapillary retinal perfusion related to myopia in healthy eyes? A prospective comparative study. BMJ open. 2016;6(3):e010791.
23. Leveque PM, Zeboulon P, Brasnu E, Baudouin C, Labbe A. Optic Disc Vascularization in Glaucoma: Value of Spectral-Domain Optical Coherence Tomography Angiography. Journal of ophthalmology. 2016;2016:6956717. [PubMed: 26998352]
24. Hollo G Vessel density calculated from OCT angiography in 3 peripapillary sectors in normal, ocular hypertensive, and glaucoma eyes. European journal of ophthalmology. 2016;26(3):e42–5. [PubMed: 26692060]
25. Gao SS, Liu G, Huang D, Jia Y. Optimization of the split-spectrum amplitude-decorrelation angiography algorithm on a spectral optical coherence tomography system. Opt Lett. 2015;40(10):2305–8. [PubMed: 26393725]
26. Siesky B, Harris A, Brizendine E, Marques C, Loh J, Mackey J, et al. Literature review and meta-analysis of topical carbonic anhydrase inhibitors and ocular blood flow. Surv Ophthalmol. 2009;54(1):33–46. [PubMed: 19171209]

Table 1.

Demographic and Ocular Characteristics of 37 Study Participants

Characteristic	No. (%)*
Age, yrs (mean ± SD)	63.8 ± 12.9
Gender	
Male	23 (62)
Female	14 (38)
CCT, μm (mean ± SD)	540.2 ± 37.1
Number of glaucoma drops	0.79 ± 1.2
OCT average RNFL thickness, μm (mean ± SD)	79.8 ± 20.3
Visual field mean deviation, dB (mean ± SD)	−4.9 ± 4.4
Visual field square of loss variance, dB (mean ± SD)	3.9 ± 2.6

*Where applicable.

CCT = central corneal thickness; D = diopters; IOP = intraocular pressure; SD = standard deviation;

Table 2a:

Effect of change in intraocular pressure (IOP) and signal strength index (SSI) on the vessel density and structural measurements in the optic nerve head and peripapillary regions based on the mixed models (values marked in bold suggest significant associations p≤0.05).

	Effect of IOP change		Effect of SSI change	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Whole enface vessel density	0.03 (−0.09, 0.15)	0.62	**0.23 (0.19, 0.26)**	**<0.001**
Inside disc vessel density	0.07 (−0.09, 0.23)	0.39	**0.31 (0.25, 0.36)**	**<0.001**
Average Peripapillary vessel density	−0.01 (−0.16, 0.24)	0.89	**0.19 (0.14, 0.24)**	**<0.001**
Nasal vessel density	0.10 (−0.10, 0.29)	0.34	**0.16 (0.13, 0.26)**	**<0.001**
Inferonasal vessel density	0.01 (−0.25, 0.27)	0.09	**0.25 (0.16, 0.34)**	**<0.001**
Inferotemporal vessel density	0.10 (−0.16, 0.35)	0.45	**0.16 (0.08, 0.25)**	**<0.001**
Superotemporal vessel density	0.20 (−0.04, 0.44)	0.10	**0.15 (0.07, 0.23)**	**<0.001**
Superonasal vessel density	0.05 (−0.21, 0.31)	0.35	**0.30 (0.20, 0.39)**	**<0.001**
Temporal vessel density	−0.02 (−0.21, 0.18)	0.86	**0.18 (0.11, 0.24)**	**<0.001**

Table 2b:

Effect of change in intraocular pressure (IOP) and signal strength index (SSI) on the vessel density and structural measurements in the macular region based on the mixed models (values marked in bold suggest significant associations p≤0.05).

	Effect of IOP change		Effect of SSI change	
	Coefficient (95% CI)	**P value**	**Coefficient (95% CI)**	**P value**
Whole enface vessel density	0.07 (−0.06, 0.19)	0.28	**0.41 (0.36, 0.46)**	**<0.001**
Fovea vessel density	0.06 (−0.15, 0.28)	0.57	**0.27 (0.18, 0.35)**	**<0.001**
Parafovea vessel density	0.12 (−0.02, 0.26)	0.09	**0.44 (0.39, 0.50)**	**<0.001**
Superior Hemifield vessel density	0.12 (−0.04, 0.27)	0.13	**0.45 (0.39, 0.51)**	**<0.001**
Inferior Hemifield vessel density	0.13 (−0.02, 0.28)	0.08	**0.43 (0.37, 0.50)**	**<0.001**
Temporal vessel density	0.11 (−0.06, 0.28)	0.19	**0.43 (0.36, 0.50)**	**<0.001**
Superior vessel density	**0.19 (0.03, 0.36)**	**0.02**	**0.42 (0.35, 0.50)**	**<0.001**
Nasal vessel density	0.13 (−0.04, 0.30)	0.13	**0.51 (0.43, 0.58)**	**<0.001**
Inferior vessel density	0.09 (−0.09, 0.26)	0.33	**0.40 (0.33, 0.47)**	**<0.001**

Table 3a:

Signal strength index adjusted Optic Nerve vessel densities at various time points of the day.

	08:00	11:00	14:00	16:00	P value
Whole enface vessel density	**49.4 (49.1, 49.8)**	**49.7 (49.4, 50.0)**	**50.1 (49.8, 50.5)**	**50.1 (49.8, 50.5)**	**0.008**
Inside disc vessel density	49.6 (49.1, 50.2)	50.2 (49.6, 50.7)	50.6 (50.1, 51.1)	50.5 (49.9, 51.0)	0.05
Average Peripapillary vessel density	57.5 (57.1, 58.0)	58.0 (57.6, 58.5)	58.2 (57.7, 58.6)	58.5 (58.1, 58.9)	0.018
Nasal vessel density	54.0 (53.4, 54.6)	54.6 (54.0, 55.2)	54.5 (53.9, 55.1)	55.4 (54.8, 55.9)	0.01
Inferonasal vessel density	57.5 (56.7, 58.3)	57.6 (56.8, 58.5)	58.5 (57.7, 59.3)	58.4 (57.6, 59.2)	0.196
Inferotemporal vessel density	60.2 (59.5, 61.0)	60.3 (59.6, 61.1)	60.9 (60.1, 61.6)	61.5 (60.7, 62.2)	0.080
Superotemporal vessel density	60.1 (59.4, 60.8)	60.9 (60.1, 61.6)	60.9 (60.2, 61.6)	60.9 (60.2, 61.6)	0.276
Superonasal vessel density	54.8 (53.9, 55.6)	55.8 (54.9, 56.6)	55.8 (54.9, 56.6)	56.2 (55.4, 57.1)	0.106
Temporal vessel density	60.7 (60.1, 61.3)	61.0 (60.4, 61.6)	61.1 (60.5, 61.6)	61.0, 61.6)	0.813

Table 3b:

Signal strength index adjusted Macula vessel densities at various time points of the day.

	08:00	11:00	14:00	16:00	P value
Whole enface vessel density	44.7 (44.3, 45.1)	44.9 (44.5, 45.3)	45.4 (44.5, 45.3)	45.0 (44.6, 45.4)	0.135
Fovea vessel density	31.0 (30.2, 31.8)	31.6 (30.8, 32.3)	31.8 (31.0, 32.6)	31.3 (30.5, 32.1)	0.492
Parafovea vessel density	47.8 (47.2, 48.4)	48.2 (47.6, 48.8)	48.6 (48.0, 49.2)	47.8 (47.3, 48.4)	0.171
Superior Hemifield	48.1 (47.4, 48.7)	48.4 (47.7, 49.0)	48.8 (48.1, 49.4)	48.1 (47.4, 48.8)	0.42
Inferior Hemifield	47.5 (46.9, 48.1)	48.0 (47.4, 48.7)	48.5 (47.9, 49.1)	47.6 (47.0, 48.2)	0.10
Temporal	48.8 (48.1, 49.5)	49.2 (48.5, 50.0)	49.2 (48.5, 50.0)	48.8 (48.1, 50.0)	0.71
Superior	48.1 (47.3, 48.9)	48.3 (47.4, 49.1)	48.7 (47.9, 49.5)	48.3 (47.5, 49.1)	0.78
Nasal	**47.5 (46.8, 48.3)**	**48.1 (47.4, 48.9)**	**48.9 (48.2, 49.7)**	**47.5 (46.8, 48.3)**	**0.03**
Inferior	46.8 (46.0, 47.5)	47.2 (46.5, 47.9)	47.7 (47.0, 48.4)	46.8 (46.0, 47.5)	0.22

Table 4.

Repeatability estimates of peripapillary and macular vessel density measurements. Figures in the parenthesis represents 95% confidence limits.

Parameter	Sw (%)	CRw (%)	CVw (%)
Peripapillary Vessel density			
Whole enface disc	1.7 (1.6, 1.9)	4.8 (4.4, 5.3)	3.7 (3.3–4.2)
Inside disc	2.7 (2.5, 3.0)	7.5 (6.8, 8.2)	5.6 (4.7, 6.4)
Peripapillary	2.0 (1.8, 2.2)	5.5 (5.0, 6.0)	3.7 (3.1–4.2)
Macular Vessel density			
Whole enface macula	2.6 (2.3, 2.8)	7.1 (6.5, 7.8)	5.7 (4.9–6.5)
Parafovea	3.2 (2.9, 3.5)	8.9 (8.1, 9.8)	6.8 (5.9–7.6)

Sw: within subject standard deviation; CRw: coefficient of repeatability; CVw: coefficient of variation.