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Effect of Scan Size on Glaucoma Diagnostic Performance using OCT Angiography En Face Images of the Radial Peripapillary Capillaries

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Abstract

Objective: To compare diagnostic ability of peripapillary vessel parameters from 4.5×4.5mm (“4.5”) and 6.0×6.0mm (“6.0”) spectral-domain optical coherence tomography angiography (SD-OCTA) scans of the radial peripapillary capillaries (RPC) in detecting primary open angle glaucoma (POAG) from non-glaucoma eyes.

Methods: Consecutive patients from an academic glaucoma clinic underwent 4.5 and 6.0 scans (CIRRUS™ HD-OCT 5000 with AngioPlex® OCT Angiography; ZEISS, Dublin, CA). Automatic segmentation created *en face* RPC images. Vessel area density (VAD), vessel skeleton density (VSD), and flux were calculated using custom quantification software, and perfusion density (PD) and flux index (FI) using automated quantification software. Area under curve (AUC) statistics included age and hypertension in the analysis.

Results: Of 173 eyes from 123 patients who underwent both 4.5 and 6.0 imaging, 32 POAG eyes from 32 patients and 95 non-glaucoma eyes from 95 patients were studied. For the global region of 4.5 versus 6.0 scans, AUC was 0.940 and 0.916 for VAD ($p=0.286$); 0.941 and 0.921 for VSD ($p=0.385$); 0.942 and 0.916 for flux ($p=0.239$); 0.912 and 0.884 for PD ($p=0.103$); and 0.913 and 0.865 for FI ($p=0.159$), respectively. For the quadrant regions, 4.5 images significantly outperformed 6.0 images for the superior and inferior quadrants for flux and superior and nasal quadrants for FI ($P_s = 0.007, 0.047, 0.011, 0.007$, respectively); other quadrant differences were not significant.

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Conclusions: Parameters from 4.5 scans generally outperformed those from 6.0 scans in the global and quadrant regions, suggesting greater digital resolution in 4.5 scans of the immediate peripapillary RPC is important in detecting glaucomatous changes.

Precis:

When comparing 4.5×4.5mm to 6.0×6.0mm optical coherence tomography angiography scans of the radial peripapillary capillaries for glaucoma diagnostic capability, there was a trend of 4.5 scans outperforming 6.0 scans, especially for inferior, nasal, and superior quadrants.

Keywords

OCT Angiography; glaucoma; diagnostic accuracy; scan size

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide.¹ The group of eye diseases is characterized by progressive deterioration and loss of retinal ganglion cells (RGCs) and their axons (retinal nerve fiber layer; RNFL).² Clinical diagnosis is usually made after evaluating the optic disc on eye exam, visual field (VF) test, and optical coherence tomography (OCT) testing.^{2–4} Previous studies have shown that early glaucomatous damage can be detected as reduced RNFL thickness in the peripapillary region by OCT^{4–6}, but it is not without limitations.

Optical coherence tomography angiography (OCTA) is a relatively new, non-invasive imaging technique that is used to quantitatively evaluate *in vivo* microvascular perfusion in various retinal layers with repeatable and reproducible measurements.^{7–11} While many studies^{12–18} have consistently demonstrated reduced peripapillary perfusion in glaucoma patients using OCTA, recent studies^{9,13–15,17,19–21} have shown variable diagnostic ability of peripapillary vascular parameters to detect glaucoma. While this variability could result from differences in OCTA hardware, segmentation algorithms, or quantification software, it is also possible that the diagnostic variability may be due to differences in scan sizes. Larger scan sizes cover a larger anatomic area that may provide valuable information about more peripheral superficial retinal vasculature, but in many instances, including in our study, the smaller scan size, though covering a smaller peripapillary anatomic area, has higher digital resolution. Thus, it is not clear which scan sizes have the diagnostic advantage for glaucoma.

Many OCTA studies have used different scan sizes, including 3.0×3.0mm^{9,13}, 4.5×4.5mm^{14,17,19,22–26}, 6.0×6.0mm^{20,21,27}, and 6.72×6.72mm¹⁵, to assess diagnostic ability of optic nerve head (ONH) and peripapillary perfusion parameters, but there have not been direct comparisons of various scan sizes within the same study population. Understanding the effect of OCTA image size on diagnostic ability of peripapillary vascular parameters will help inform optimal image acquisition both for glaucoma clinical care and design of glaucoma research studies. The purpose of our study was to compare the diagnostic accuracy of perfusion parameters between 4.5×4.5mm (“4.5”) and 6×6mm (“6.0”) scans specifically for perfused radial peripapillary capillaries (RPCs) using an automated segmentation protocol on the spectral domain-OCTA (SD-OCTA) in

differentiating primary open-angle glaucoma (POAG) from non-glaucoma eyes in a glaucoma clinic population. We assessed custom research-oriented quantification software and automated clinic-oriented quantification software, which is not yet commercially available, in this analysis.

METHODS

Study Group Selection and Clinical Assessment

An observational, cross-sectional study was performed on consecutive willing patients presenting to the glaucoma service at USC Roski Eye Institute, Keck Medicine of University of Southern California from January 1, 2017 to May 31, 2018. Secondary glaucoma and angle closure glaucoma were excluded. The research protocol was approved by the institutional review board of the University of Southern California (USC) and carried out in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects following an explanation of the nature and intent of the study.

The diagnosis of POAG was based on assessment by a fellowship-trained glaucoma specialist, incorporating a clinical exam demonstrating an optic nerve rim defect (notching or localized thinning) characteristic of glaucoma. RNFL thickness and deviation maps from OCT (CIRRUS™ HD-OCT 5000 with AngioPlex® OCT Angiography; ZEISS, Dublin, CA) were retrospectively reviewed on all patients. POAG severity was determined based on Hodapp-Parrish-Anderson criteria.^{28,29} Non-glaucoma participants in the study had clinical exam results that ranged from normal to glaucoma suspect and had non-glaucomatous optic discs. Inclusion criterion for both glaucoma and non-glaucoma groups included age ≥ 21 years. Exclusion criteria included other optic nerve or retinal diseases, history of ocular trauma or ocular surgeries other than uncomplicated cataract and glaucoma surgery, signal strength < 7 (out of 10), and poor image quality from motion artifacts, significant decentration, or media opacities, such as vitreous floaters. One eye from each subject was included in the study. When both eyes met the study criteria, the eye with the higher signal strength index and image quality was selected.

All subjects underwent slit lamp biomicroscopy, intraocular pressure (IOP) measurement using Goldman applanation tonometry, VF testing (24–2 SITA Standard, HFA™ II-I; ZEISS), OCT imaging of RNFL thickness (CIRRUS HD-OCT 5000; ZEISS), and OCTA imaging (ZEISS AngioPlex OCT Angiography) acquiring 4.5 and 6.0 scans of the peripapillary region. The A-scan spacing for 4.5 scans was approximately 12.86µm while that for 6.0 scans was approximately 17.14µm, with both scans having a total of 350×350 A-scans.

Demographic information collected from the clinical chart included age, sex, diagnoses of diabetes or hypertension, glaucoma medications, prior ocular surgeries, IOP, central corneal thickness, cup to disc ratio (CDR), mean global and quadrant RNFL thicknesses (along the 3.4mm-diameter circle centered on the nerve), VF MD, and VF pattern standard deviation (PSD) in glaucomatous and non-glaucomatous eyes.

OCTA Image Analysis

Automated segmentation software (ZEISS) detected the boundaries of the retinal layers from the structural OCT cross-sectional images by measuring the gradient of OCT signals. The boundaries of the RNFL as defined by this automated segmentation were applied to the motion volume generated by OCT microangiography using the complex OCT signal (OMAG)³⁰ to create RPC *en face* images (Figure 1).

Following this, a custom quantification software³⁰ with an interactive interface was used to quantify three measures of the microvasculature for the global and quadrant peripapillary regions (MATLAB R2017a; MathWorks Inc, Natick, MA, USA) (Figure 2). The global OCTA parameter measurements were based on the entire 4.5 and 6.0 scans. The quadrant OCTA parameter measurements were based on temporal, superior, nasal, and inferior sections within the annulus of inner diameter of 2mm and outer diameters of 4.5mm and 6.0mm centered on ONH on the 4.5 and 6.0 scans, respectively. The original grayscale *en face* OCTA images of the 4.5 and 6.0 scans were converted to binary vessel maps using a three-way combined method consisting of global thresholding, Hessian filter, and adaptive threshold (Figure 1). The area within the ONH was selected to establish the baseline background noise for global thresholding and then was blacked out for quantification. Vessel skeleton maps were created by linearizing vessel signals into 1-pixel width. Three-vessel parameters provided distinct and biologically relevant information about microvasculature perfusion in the peripapillary region. Large vessels of more than 32μm were removed from the image area to be quantified.

Vessel area density (VAD) provided information about both medium vessels and capillaries. From the binary vessel map, VAD was the unitless proportion of total sum area of white pixels with detected OCTA signal ($A_{(I,j)}$) divided by the total sum area of all pixels in the binarized image ($X_{(I,j)}$), excluding the areas occupied by the vessels larger than 32μm.

$$VAD = \frac{\sum_{i=1, j=1}^n A_{(i,j)}}{\sum_{i=1, j=1}^n X_{(i,j)}}$$

Vessel skeleton density (VSD) was considered a marker for perfused capillary density. VSD was the sum of white pixels in the vessel skeleton map from linearized OCTA signal ($S_{(I,j)}$) divided by the sum of all pixels in the vessel skeleton map ($X_{(I,j)}$).

$$VSD = \frac{\sum_{i=1, j=1}^n S_{(i,j)}}{\sum_{i=1, j=1}^n X_{(i,j)}}$$

Flux measured the number of blood cells passing through a retinal vessel cross-sectional area per unit time. The flux was the unitless, mean flow intensity in the vessel area, where the sum of all pixels identified as blood flow in the binary vessel map ($I_{flow(i)}$), was divided

by the total of white pixel counts on the binary vessel map (n) multiplied by the full dynamic range of blood flow signal intensity (255).

$$\text{Flux} = \frac{\sum_{i=1}^n I_{\text{flow}(i)}}{255 * n}$$

In addition to the custom quantification software, an automated quantification software (CIRRUS 11.0; ZEISS) created for future commercial use was utilized to quantify retinal vascular density and flux for the global and quadrant peripapillary regions limited to an annulus with an inner diameter of 2mm and outer diameters of 4.5mm and 6mm, respectively in 4.5 and 6.0 scans. Perfusion density (PD) was the total area of perfused capillary vasculature per unit area in a region of interest using the RPC *en face* images. Flux index (FI) was the total area of perfused vasculature per unit area in a region of interest, weighted by the brightness of flow signal and corrected for dimmer areas on B-scan, using the RPC *en face* images.

Statistical Analysis

SAS 9.4 (Cary, NC), STATA 15.1 (College Station, TX), and Microsoft Excel 2016 (Redmond, WA) were used for all data analyses. Linear regression was used to compare the differences in continuous demographic variables between the POAG and non-glaucoma groups, controlling for age. Logistic regression was used to compare the differences in categorical demographic variables between the two groups, controlling for age. All tests were two-sided and used a significance level of 0.05. Receiver-operating-characteristics curve statistics, specifically area under the curve (AUC), were calculated to assess diagnostic accuracy and included age and hypertension in the analysis. Logistic regression model with the dependent variable as glaucoma and independent variables as OCT and OCTA parameters, age, and hypertension was used to generate predicted probabilities of glaucoma and determine sensitivities at fixed levels of specificities. DeLong's method was used to nonparametrically compare the AUCs among OCT and OCTA parameters with the predicted probabilities of glaucoma between the two groups.³¹ Two-way mixed intraclass correlations were calculated to test the agreement of quantification results between repeated testing by the same operator (test-retest reliability) and between two operators (intergrader reliability) based on a subset of 8 non-glaucoma and 8 glaucoma eyes.

RESULTS

Of 173 eyes from 123 patients who underwent both 4.5 and 6.0 SD-OCTA peripapillary imaging and met our inclusion and exclusion criteria, 32 eyes from 32 POAG patients and 91 non-glaucoma eyes from 91 control subjects were studied. The other eyes were excluded because we included only one eye per subject. 15 eyes had mild POAG, of which 6 were pre-perimetric, and 17 eyes had moderate-severe POAG, according to the Hodapp-Parrish-Anderson criteria^{28,29}. While all glaucoma cases demonstrated focal RNFL thinning consistent with the funduscopy disc findings, only two of the non-glaucoma patients demonstrated focal RNFL thinning, which the examining glaucoma specialist determined

was not consistent with the funduscopy examination. Additionally, 5 non-glaucoma patients had abnormal VF findings. However, of these 5 eyes, 4 eyes had healthy optic nerves, and one eye had a history of occipital lobe infarction causing homonymous hemianopia with healthy optic nerve. Finally, five other non-glaucoma patients were treated with glaucoma eye drops. These eyes were glaucoma suspects with ocular hypertension but healthy optic nerves.

The average age was 59 years in the POAG group and 47 years in the non-glaucoma group ($P=0.001$). There were no significant differences in sex, diabetes, or IOP between the POAG and non-glaucoma groups, controlling for age (Table 1). As expected, the glaucoma eyes had significantly thinner central corneas, greater CDR, and higher magnitudes of VF MD and PSD than the non-glaucoma eyes, controlling for age. Because the glaucoma group had significantly higher hypertension frequency than the glaucoma group ($P=0.032$), both age and hypertension were adjusted for in our AUC analysis.

There were significantly reduced VAD, VSD, flux, PD, and FI values in the RPC microcirculation in the POAG compared to non-glaucoma groups for global and all quadrant regions except nasal PD ($P=0.072$), controlling for age (Table 2). When evaluating the RNFL thickness along the entire 3.4mm diameter circle and in each of the quadrants, there were significantly lower RNFL thicknesses in POAG eyes compared to non-glaucoma eyes for all regions except the temporal quadrant ($P=0.095$). The test-retest reliability and intergrader reliability calculated by two-way mixed intraclass correlation was >0.999 for all peripapillary OCTA parameters.

Table 3 demonstrates the diagnostic accuracy and sensitivities at 80% and 90% specificities of each of the global OCTA and OCT parameters to differentiate all severities of POAG from non-glaucoma eyes. Global OCTA parameters from the 4.5 scans using the custom and automated quantification software generally showed higher AUC values and sensitivities at both specificities than the corresponding values from the 6.0 scans for detection of all glaucoma severities. The diagnostic accuracies for OCTA parameters in the detection of mild POAG were higher in the 4.5 versus the 6.0 scans, and these differences were significant for VAD, VSD, and flux ($P_s=0.023, 0.040, 0.037$). Diagnostic accuracies of RNFL thickness were 0.880, 0.915, and 0.874 for detection of any POAG, mild POAG, and moderate-severe POAG eyes, respectively. The OCTA parameter AUC values and sensitivities at both specificities were generally higher than the corresponding values for RNFL thicknesses in differentiating all glaucoma severities. However, there were no significant differences in the diagnostic accuracies between the OCTA parameters and RNFL thicknesses.

Table 4 reports the diagnostic accuracy of each of the quadrant OCTA and OCT parameters in differentiating between any POAG and non-glaucoma eyes. The AUC values of the 4.5 scans for the quadrant regions from the custom and automated quantification software were generally higher than the corresponding values for 6.0 scans. There were no significant differences in the diagnostic accuracies between the OCTA parameters from 4.5 and 6.0 scans, except for superior and inferior flux and superior and nasal FI ($P_s=0.007, 0.047, 0.011, 0.007$), which were all higher in the 4.5 scans. Diagnostic accuracies of RNFL

thickness were 0.723, 0.858, 0.742, and 0.911 for temporal, superior, nasal, and inferior peripapillary regions, respectively. The OCTA parameter AUC values were generally higher than the corresponding values for RNFL thicknesses. Nevertheless, there were no significant differences in the diagnostic accuracies between the OCTA parameters and RNFL thicknesses in all quadrant peripapillary regions except the temporal ($P=0.017$ and 0.024 for 4.5 and 6.0 VAD, respectively, 0.020 for 6.0 VSD, 0.002 and 0.004 for 4.5 and 6.0 FI, respectively) and nasal regions ($P=0.005$ for 4.5 FI), where the AUC values of the OCTA parameters were higher than those of RNFL thickness, and the inferior region ($P=0.033$ for 6.0 PD) with lower OCTA AUC.

DISCUSSION

In this study, the diagnostic accuracies for detection of glaucoma, as measured by AUC, of the various perfusion parameters from the 4.5 scans in the global RPC region trended towards better performance than those from the 6.0 scans using both custom research-oriented quantification software and automated clinic-oriented software. The diagnostic accuracies for the global scan region for detection of any POAG ranged from 0.940 to 0.942 on the 4.5 scans compared to 0.916 to 0.921 on the 6.0 scans using the custom quantification software, and 0.912 to 0.913 on the 4.5 scans compared to 0.865 to 0.884 on the 6.0 scans using the automated quantification software. The diagnostic accuracies of the quadrant regions for the 4.5 scans also trended towards being higher than those for the 6.0 scans, with significant differences between the AUC values for the superior and inferior quadrants for flux and the superior and nasal quadrants for FI. The diagnostic accuracies of both 4.5 and 6.0 scans within the quadrant regions were highest for inferior and superior regions, similar to the findings in previous studies^{19,21,23}. The consistent trend of higher diagnostic accuracy for the 4.5 scans may be explained by their better digital resolution and suggests that the more peripheral peripapillary region covered by the 6.0 scan may not provide additional diagnostic utility.

It was interesting that while there was not much difference between 4.5 versus 6.0 scan sizes in detection of moderate-severe POAG, the diagnostic accuracy for detection of mild POAG seemed to be better in the 4.5 compared to the 6.0 scan size.

These results may further suggest that the increased digital resolution in the 4.5 scans may aid in the detection of early, more subtle vascular changes present in mild POAG, as compared to the 6.0 scans.

A few other studies have recently reported diagnostic accuracy of OCTA vessel density for various image sizes in the peripapillary region. These studies differed from ours in the use of only 4.5 scans^{14,17,19,22–26}, 6.0 scans^{20,21,27}, or 6.72×6.72mm montage scans¹⁵, exclusion of glaucoma suspects from the control group^{14,15,17,19–27}, exclusion of pre-perimetric eyes from the glaucoma group^{14,15,20,23,26}, retinal layers that were examined²¹, and inclusion of large vessels in the quantification of OCTA parameters^{14,19,22,25}. Similar to the current study, Yarmohammadi et al.¹⁴ showed AUC values of 0.94 and 0.70 for vessel density (VD) in differentiating POAG and glaucoma suspect eyes, respectively, from control eyes for the entire 4.5×4.5mm RPC scans, and Chen et al.¹⁷ reported AUC value of 0.93 and 0.89 for VD

from the 4.5×4.5mm RPC scans in the global and 750-μm-wide elliptical annulus regions, respectively, discriminating between POAG (excluding pre-perimetric eyes) and healthy eyes. Additionally, Triolo et al. demonstrated AUC values of 0.506, 0.829, and 0.875 for VD on the entire 6×6mm RPC scans taken on the swept-source Plex-Elite device for control vs. glaucoma suspects, glaucoma suspects vs. POAG, and control vs. POAG, respectively.²⁰ Richter et al. had also found an AUC of 0.868 for VAD of the 6.0×6.0mm RPC scans using a more manual segmentation of the RPC layer.²⁷ Furthermore, Chen et al. showed AUCs of 0.82 and 0.60 for the 6.72×6.72mm montage scans for normal vs. glaucoma and normal vs. glaucoma suspect, respectively.¹⁵ The literature supports our findings that the diagnostic ability of the 4.5×4.5mm scans consistently trends towards being highest out of all scan sizes. The 4.5×4.5mm scan size seems to represent the optimal balance of including a larger peripapillary area than that afforded by the 3×3mm scans, which end up being largely predominated by the optic disc itself, and having a higher digital resolution than that typically afforded by the 6×6mm or 6.72×6.72mm scans.

In comparing the flux-based parameters (flux, FI) to the vessel density-based parameters (VAD, VSD, PD) for both scan sizes, there appeared to be no significant diagnostic advantage to either type of parameter. Flux measures the mean flow intensity in the vessel area, which can be interpreted as a measure of the number of red blood cells passing an area per unit time; whereas the vessel density parameters look at density of perfused vasculature at a particular threshold, without regard to fluid dynamics. For both parameters, large vessels were excluded from the calculation. While our data did not show a diagnostic advantage to flux parameters, continued improvements in the algorithms to measure fluid dynamics may serve to improve diagnostic accuracy in the future.

Additionally, as a comparison tool, we evaluated the diagnostic accuracies of mean global and quadrant RNFL thickness (on the 3.4mm circle centered on the nerve) for detection of glaucoma. The diagnostic accuracy of RNFL thickness was highest for inferior, global, then superior regions, which is consistent with prior studies demonstrating the utility of global RNFL thicknesses and our understanding that glaucoma damage tends to occur inferiorly and superiorly.^{5,21,25,32} Interestingly, while the differences between the diagnostic accuracies of RNFL thickness and OCTA perfusion parameters were mostly insignificant, as seen in previous studies^{13,14,17,20,25–27}, there was an overall trend of OCTA parameters outperforming RNFL thickness. This is consistent with findings by Yarmohammadi et al.^{14,23}, but not with several other studies^{13,14,25–27}. Specifically, there was significant outperformance within the same anatomic regions of OCTA compared to RNFL thickness for 4.5 VAD and FI and 6.0 VAD, VSD, and FI in the temporal region and 4.5 FI in the nasal region. In the superior and inferior regions, there were no significant differences in the AUC values for the OCTA parameters compared to those for RNFL thickness, except for 6.0 PD, for which RNFL outperformed the OCTA parameter. The relative differences between OCTA AUC values with respective RNFL thickness AUC values of the same cohort likely vary between studies depending on the OCTA segmentation and quantification algorithms used. While OCT algorithms have been more stable in recent years, OCTA technology is rapidly evolving. For example, Richter et al. demonstrated a higher RNFL AUC relative to the VAD AUC using a more manual segmentation technique for the RPC layer.²⁷ The current study used a more refined automatic segmentation of the RPC layer as well as

further optimized quantification software compared to the first study. This is interesting and demonstrates that continued improvements in OCTA technology could make OCTA more useful than OCT for glaucoma diagnosis. Further research is needed to understand how and whether OCTA microcirculation data could be more helpful than OCT RNFL thickness data in the diagnosis of glaucoma.

Our study reported the results of both research-oriented custom quantification software and clinic-oriented automated quantification software. To our knowledge, there have not been other studies assessing both types of quantification software. The custom software required manual operation with the user identifying the optic disc for each image analyzed. In contrast, the automated software was built into the *en face* generation software, was designed for clinic use, and automatically selected the boundary of the optic disc to be omitted without any user prompts. While both the custom software and the automated software had overall good to excellent diagnostic accuracies, the custom software trended towards higher AUCs for all global parameters. This suggests a potential diagnostic advantage to the custom software, but the automated software performed almost as well and is more practical for a clinical use setting.

Our study presents some limitations. These include the potentially confounding effect of eye drops and glaucoma procedures on retinal microcirculation in both glaucoma and non-glaucoma groups. Future research should investigate the effects of these glaucoma-related interventions on retinal perfusion. Moreover, our study had differences in mean age and hypertension frequency between glaucoma and non-glaucoma groups, but both age and hypertension were included in our AUC calculation. Overall, our study population consisted of consecutive patients from an academic glaucoma setting, including glaucoma suspects, so the diagnostic accuracy is likely representative of a real-life glaucoma clinic setting.

In conclusion, we found that microcirculation in the RPC network for both 4.5 and 6.0 scans were significantly reduced in glaucoma patients. Peripapillary perfusion parameters of the 4.5 scans had excellent diagnostic performance with flux in the superior and inferior quadrants significantly outperforming those of the 6.0 scans. Overall, our results support the idea that the higher digital resolution of the RPCs in the 4.5 scans are important in optimizing detection of glaucomatous microvasculature changes. Additional research should refine imaging algorithms in the RPC network and investigate the reproducibility of quantitative OCTA in the evaluation of glaucoma.

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Figure 1.

(Top row) 4.5×4.5 (left) and 6×6 (right) OCTA *en face* images with annulus of inner diameter of 2mm and outer diameters of 4.5 mm and 6mm, respectively, centered on optic nerve head and (Bottom row) corresponding binary vessel maps. S=Superior. T=Temporal. I=Inferior. N=Nasal.

Figure 2.
Overview of OCTA quantification using the custom quantification software

Table 1.

Demographic and Clinical Characteristics of the Non-Glaucoma and Glaucoma Eyes

Variables	Non-Glaucoma (91 eyes of 91 patients)	Glaucoma (32 eyes of 32 patients)	P-Value ^o
Age (years)	47 (18) [^]	59 (16)	0.001
Female Sex	52 (57%)	14 (44%)	0.144
Diabetes	9 (9.9%)	3 (9.4%)	0.378
Hypertension	12 (13%)	14 (44%)	0.032
Number Glaucoma Medications	0.07 (0.29)	1.47 (1.40)	<0.001
Timolol	1 (1%)	10 (31%)	0.003
Brimonidine	1 (1%)	7 (22%)	0.007
Prostaglandin Analogues	3 (3%)	20 (63%)	<0.001
Carbonic Anhydrase Inhibitors	1 (1%)	10 (31%)	0.002
Prior glaucoma surgery	0	4 (13%)	-
Intraocular Pressure (mmHg)	15 (3.1)	14 (4.6)	0.206
Central Corneal Thickness (μm)	558 (40.7)	543 (39.1)	0.026
Cup-Disc Ratio	0.54 (0.21)	0.78 (0.13)	<0.001
Visual Field Mean Deviation (dB)	-1.26 (1.97)	-6.93 (6.84)	<0.001
Visual Field Pattern Standard Deviation (dB)	1.95 (1.30)	5.90 (4.11)	<0.001

[^] All data listed as mean (standard deviation) or frequency (percent).

^o P-values for continuous variables were based on linear regression and categorical variables were based on logistic regression, both controlling for age.

Table 2.

Mean Global and Quadrant Peripapillary OCTA and OCT Parameters for 4.5 and 6.0 Scans

	4.5mm×4.5mm			6.0mm×6.0mm		
<i>Parameter</i>	<i>Non-Glaucoma</i>	<i>Glaucoma</i>	<i>P-Values</i> *	<i>Non-Glaucoma</i>	<i>Glaucoma</i>	<i>P-Values</i>
<u>GLOBAL</u>						
VAD	0.469 (0.027) [^]	0.384 (0.058)	<0.001	0.364 (0.043)	0.272 (0.058)	<0.001
VSD	0.191 (0.012)	0.153 (0.026)	<0.001	0.141 (0.019)	0.099 (0.025)	<0.001
Flux	0.282 (0.025)	0.229 (0.025)	<0.001	0.251 (0.025)	0.210 (0.021)	<0.001
PD	0.447 (0.018)	0.400 (0.035)	<0.001	0.431 (0.021)	0.386 (0.034)	<0.001
FI	0.388 (0.024)	0.338 (0.032)	<0.001	0.568 (0.036)	0.513 (0.039)	<0.001
RNFL Thickness ^o	-	-	-	92.8 (10.8)	73.2 (13.3)	<0.001
<u>TEMPORAL</u>						
VAD	0.504 (0.021)	0.448 (0.070)	<0.001	0.433 (0.040)	0.354 (0.086)	<0.001
VSD	0.220 (0.011)	0.195 (0.032)	<0.001	0.183 (0.017)	0.147 (0.039)	<0.001
Flux	0.495 (0.038)	0.450 (0.036)	<0.001	0.365 (0.019)	0.351 (0.017)	0.011
PD	0.484 (0.025)	0.453 (0.034)	<0.001	0.435 (0.027)	0.415 (0.041)	0.046
FI	0.398 (0.028)	0.344 (0.038)	<0.001	0.511 (0.042)	0.446 (0.049)	<0.001
RNFL Thickness	-	-	-	64.9 (10.7)	59.0 (15.9)	0.095
<u>SUPERIOR</u>						
VAD	0.546 (0.012)	0.494 (0.060)	<0.001	0.478 (0.029)	0.393 (0.079)	<0.001
VSD	0.221 (0.006)	0.198 (0.027)	<0.001	0.193 (0.011)	0.156 (0.034)	<0.001
Flux	0.548 (0.041)	0.470 (0.042)	<0.001	0.386 (0.021)	0.359 (0.022)	<0.001
PD	0.426 (0.027)	0.377 (0.048)	<0.001	0.428 (0.034)	0.368 (0.055)	<0.001
FI	0.381 (0.022)	0.334 (0.029)	<0.001	0.634 (0.044)	0.581 (0.052)	<0.001
RNFL Thickness	-	-	-	115.0 (16.0)	88.5 (20.6)	<0.001
<u>NASAL</u>						
VAD	0.485 (0.036)	0.444 (0.057)	0.001	0.386 (0.054)	0.325 (0.059)	<0.001
VSD	0.201 (0.015)	0.183 (0.025)	<0.001	0.156 (0.023)	0.127 (0.026)	<0.001
Flux	0.478 (0.041)	0.446 (0.040)	0.007	0.359 (0.016)	0.346 (0.014)	0.001
PD	0.431 (0.025)	0.400 (0.035)	<0.001	0.405 (0.030)	0.390 (0.030)	0.072
FI	0.388 (0.028)	0.339 (0.033)	<0.001	0.520 (0.044)	0.493 (0.051)	0.033
RNFL Thickness	-	-	-	71.9 (12.2)	64.3 (11.1)	0.003

	4.5mm×4.5mm			6.0mm×6.0mm		
<i>Parameter</i>	<i>Non-Glaucoma</i>	<i>Glaucoma</i>	<i>P-Values</i> [*]	<i>Non-Glaucoma</i>	<i>Glaucoma</i>	<i>P-Values</i>
INFERIOR						
VAD	0.542 (0.015)	0.453 (0.086)	<0.001	0.484 (0.029)	0.372 (0.094)	<0.001
VSD	0.221 (0.007)	0.182 (0.037)	<0.001	0.197 (0.010)	0.147 (0.042)	<0.001
Flux	0.561 (0.040)	0.466 (0.058)	<0.001	0.395 (0.021)	0.359 (0.026)	<0.001
PD	0.444 (0.026)	0.368 (0.066)	<0.001	0.459 (0.038)	0.368 (0.068)	<0.001
FI	0.384 (0.022)	0.334 (0.036)	<0.001	0.609 (0.040)	0.552 (0.057)	<0.001
RNFL Thickness	-	-	-	119.5 (18.2)	81.0 (22.0)	<0.001

[^] All Data are listed as mean (standard deviation).

^{*} P-values were based on logistic regression, controlling for age.

^o RNFL thicknesses measured in along the 3.4mm circle centered on the optic nerve for the entire circle ("global") or for specific quadrants.

OCTA = optical coherence tomography angiography; Custom software parameters: VAD = Vessel Area Density, VSD = Vessel Skeleton Density, Flux; Automated software parameters: PD = Perfusion Density, FI = Flux Index; RNFL = Retinal Nerve Fiber Layer

Table 3.

Diagnostic Accuracy and Sensitivity of Global OCTA and OCT Parameters of Peripapillary Regions for 4.5 and 6.0 Scans by Glaucoma Severity

Parameters	Area-Under-Curve Statistic*		P-values	Sensitivity at 80% Specificity		Sensitivity at 90% Specificity	
	4.5×4.5mm	6.0×6.0mm		4.5×4.5mm	6.0×6.0mm	4.5×4.5mm	6.0×6.0mm
			4.5×4.5mm vs 6.0×6.0mm				
<u>Any POAG</u>							
VAD	0.940	0.916	0.286	87.5%	81.3%	78.1%	65.6%
VSD	0.941	0.921	0.385	87.5%	81.3%	84.4%	65.6%
Flux	0.942	0.916	0.239	90.6%	84.4%	78.1%	68.8%
PD	0.912	0.884	0.103	75.0%	81.3%	68.8%	65.6%
FI	0.913	0.865	0.159	87.5%	78.1%	65.6%	53.1%
RNFL Thickness	-	0.880	-	-	83.3%	-	66.7%
<u>Mild POAG</u>							
VAD	0.944	0.882	0.023	93.3%	73.3%	86.7%	53.3%
VSD	0.948	0.893	0.040	93.3%	73.3%	86.7%	53.3%
Flux	0.951	0.899	0.037	93.3%	73.3%	80.0%	60.0%
PD	0.869	0.831	0.259	66.7%	60.0%	53.3%	40.0%
FI	0.922	0.878	0.193	86.7%	80.0%	66.7%	53.3%
RNFL Thickness	-	0.915	-	-	84.6%	-	69.2%
<u>Moderate-Severe POAG</u>							
VAD	0.948	0.952	0.869	82.4%	94.1%	82.4%	76.5%
VSD	0.945	0.956	0.669	82.4%	94.1%	82.4%	76.5%
Flux	0.942	0.937	0.866	88.2%	82.4%	76.5%	76.5%
PD	0.960	0.945	0.374	88.2%	94.1%	82.4%	82.4%
FI	0.915	0.860	0.285	82.4%	76.5%	58.8%	52.9%
RNFL Thickness	-	0.874	-	-	82.4%	-	76.5%

* Included age and hypertension in the analysis.

OCTA = optical coherence tomography angiography; POAG = primary open angle glaucoma; Custom software parameters: VAD = Vessel Area Density, VSD = Vessel Skeleton Density, Flux; Automated software parameters: PD = Perfusion Density, FI = Flux Index; RNFL = Retinal Nerve Fiber Layer

Table 4.

Diagnostic Accuracy of Quadrant OCTA and OCT Parameters of Peripapillary Regions for 4.5 and 6.0 Scans for Detection of Any POAG

	<i>Area-Under-Curve Statistic*</i>		<i>P-Values</i>
<i>Parameter</i>	<i>4.5×4.5mm</i>	<i>6.0×6.0mm</i>	<i>4.5s4.5mm vs 6.0×6.0mm</i>
<u>TEMPORAL</u>			
VAD	0.838	0.836	0.948
VSD	0.817	0.839	0.635
Flux	0.816	0.768	0.141
PD	0.794	0.718	0.098
FI	0.899	0.868	0.372
RNFL Thickness	0.723	-	-
<u>SUPERIOR</u>			
VAD	0.888	0.859	0.324
VSD	0.868	0.859	0.772
Flux	0.909	0.843	0.007
PD	0.840	0.836	0.883
FI	0.921	0.822	0.011
RNFL Thickness	0.858	-	-
<u>NASAL</u>			
VAD	0.786	0.810	0.443
VSD	0.785	0.826	0.202
Flux	0.766	0.788	0.514
PD	0.801	0.716	0.055
FI	0.884	0.751	0.007
RNFL Thickness	0.742	-	-
<u>INFERIOR</u>			
VAD	0.915	0.881	0.180
VSD	0.927	0.895	0.280
Flux	0.913	0.862	0.047
PD	0.876	0.883	0.717
FI	0.908	0.833	0.072

	<i>Area-Under-Curve Statistic</i> [*]		<i>P-Values</i>
<i>Parameter</i>	<i>4.5×4.5mm</i>	<i>6.0×6.0mm</i>	<i>4.5s4.5mm vs 6.0×6.0mm</i>
RNFL Thickness	0.911	-	-

^{*} Included age and hypertension in the analysis.

OCTA = optical coherence tomography angiography; POAG = primary open angle glaucoma; Custom software parameters: VAD = Vessel Area Density, VSD = Vessel Skeleton Density, Flux; Automated software parameters: PD = Perfusion Density, FI = Flux Index; RNFL = Retinal Nerve Fiber Layer