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Referenced scans improve the repeatability of optical coherence tomography angiography measurements in normal and glaucoma eyes

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Abstract

Aim: To compare the repeatability of peripapillary perfusion density and flux index measurements on referenced and non-referenced optical microangiography (OMAG) scans in normal, glaucoma suspect and glaucoma eyes.

Methods: In a cross-sectional study, 48 eyes (33 subjects) underwent 3 repeat, non-referenced peripapillary OMAG scans in the same session and 43 eyes (25 subjects) underwent 3 referenced peripapillary OMAG scans. In the referenced scan group, repeat scans (second and the third scan) were acquired exactly on the baseline (first) scan using the “track to prior scan” option on the device. Repeatability estimates of the mean and 4-sector (temporal, superior, nasal and inferior) OMAG measurements on the non-referenced and referenced scans were assessed using within-subject coefficient of repeatability (CRw) and variation (CVw).

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I am one author signing on behalf of all co-owners of the Contribution.

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Competing interests: None.

Ethics Committee Approval: Obtained from Ethics Committee of Narayana Nethralaya.

Results: CRw (%) of peripapillary perfusion density measurements (range: 2.0 to 4.1) on non-referenced scans were significantly higher than that on referenced scans (range: 1.4 to 2.7). CVw (%) ranged from 1.7 to 3.1 on non-referenced scans and 1.2 to 2.1 on referenced scans. CRw of flux index on non-referenced scans ranged from 4.4 to 5.8 and on referenced scans from 3.6 to 4.8. CVw on non-referenced and referenced scans ranged from 4.1 to 5.2 and from 3.3 to 4.5 respectively.

Conclusions: Repeatability estimates of OMAG measurements were better on referenced compared to non-referenced scans. Perfusion density measurements had lower variability than flux index. OCTA-measured perfusion density of referenced scans are preferable for monitoring vascular change in glaucoma.

Keywords

glaucoma; optical microangiography; optical coherence tomography angiography; referenced scan; coefficient of variation; coefficient of repeatability

INTRODUCTION

Optical coherence tomography angiography (OCTA) is used to visualize and quantify the retinal vasculature.[1] Multiple studies have reported a reduction in the OCTA-measured superficial peripapillary and macular vessel densities in eyes with glaucoma.[2–5] In addition, multiple studies have also reported the ability of OCTA to predict the risk of glaucoma progression.[6–8] As OCTA is a relatively recent technology, there are not many long-term studies evaluating its ability to detect progressive vascular changes in glaucoma. However, a few case reports[9, 10] and case series[11, 12] have showed that OCTA is capable of detecting a progressive decrease in superficial vessel densities in glaucomatous eyes even when is monitored over short periods of time.

An important characteristic of any test that is used to detect measurement change over time is the test-retest variability; this is a major factor in determining the clinical utility of the test to diagnose progression. In this regard, a major limitation of using OCTA to detect progressive vascular changes in glaucoma is the high test-retest variability of vessel density measurements. A recent study compared the test-retest variability of OCTA-measured vessel density with that of OCT-measured retinal nerve fiber layer (RNFL) thickness,[13] the latter being a standard test to monitor progressive structural changes in glaucoma. The intra-visit and inter-visit coefficient of variation (a measure of variability) of average RNFL thickness was 1.5%, while that of average peripapillary vessel density was close to 4.0% ($P < 0.001$). [13]

A recent advance with OCT scanning is the option to “track to prior scan”. This enables the follow-up scans to be acquired exactly on baseline scan (referenced scans). It is thought that this option reduces the test-retest variability of OCTA measurements. With this hypothesis, the purpose of the current study was to compare the test-retest variability of the OCTA measurements of referenced scans to that of the non-referenced scans.

METHODS

This was a prospective, cross-sectional study conducted at Narayana Nethralaya, a tertiary eye care center in Bengaluru, South India between January 2019 and June 2019. The methodology adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all participants and the study was approved by the Ethics Committee of Narayana Nethralaya.

Participants of the study included control subjects, glaucoma suspects and glaucoma patients. Control subjects were individuals who presented for a routine eye examination. They had no family history of glaucoma, intraocular pressure (IOP) ≤21 mm Hg, open angles on gonioscopy, normal anterior and posterior segment on clinical examination by glaucoma experts and normal visual field (VF) test result. Glaucoma suspects either had an intraocular pressure >21 mmHg, or suspicious optic nerve heads (neuroretinal rim thinning or cup to disc ratio asymmetry of 0.2 or more between the 2 eyes) as assessed by glaucoma experts and normal VF test result. Glaucoma patients had focal or diffuse neuroretinal rim thinning, localized notching or retinal nerve fiber layer defects as documented by glaucoma experts on dilated examination with slit-lamp biomicroscopy and a handheld high powered convex lens, and glaucomatous VF test result (described below). All types of glaucoma patients (primary or secondary, open or angle closure) were included. Inclusion criteria for all participants were age ≥18 years, corrected distance visual acuity of 20/40 or better and refractive error within ±5 D sphere and ±3 D cylinder. Exclusion criteria were presence of any media opacities that prevented good quality OCT and OCTA scans, or any retinal or neurological disease (other than glaucoma) which could confound the evaluation. All participants underwent OCT imaging with Cirrus HD-OCT (model 5000, Carl Zeiss Meditec Inc., Dublin, CA). VF examination was performed only in glaucoma suspects and patients.

VF examination was performed using Humphrey Field analyzer 3 (model 860, Carl Zeiss Meditec Inc., Dublin, CA), with the Swedish interactive threshold algorithm (SITA) standard 24–2 program. VFs were considered reliable if the fixation losses were less than 20%, and the false positive and false negative response rates were less than 15%. VF was considered glaucomatous if the glaucoma hemifield test result was outside normal limits, pattern standard deviation was abnormal at $p<5\%$ level, or ≥3 test points in a cluster on pattern deviation probability plot were abnormal at $p<5\%$ with at least one point abnormal at $p<1\%$.

OCT scanning of all subjects was performed using the optic disc cube 200×200 scan. From these cube scans, RNFL thickness was calculated along a circle 3.46 mm in diameter positioned evenly around the center of the optic disc. Average RNFL thickness over the entire circle as well as the 4 sectors (temporal, superior, nasal and inferior) of 90 degrees each were evaluated.

OCTA of the peripapillary region was performed using Cirrus HD-OCT (software version 11.0.0.29946) by a single technician. The algorithm used to achieve blood vessel delineation on Cirrus HD-OCT is the optical microangiography (OMAG).[14] OMAG utilizes both the intensity and phase information from B scans repeated at the same position to delineate

blood vessels.[15] The peripapillary region was imaged using the 4.5×4.5 mm cube scan centered on the optic disc. This scan pattern has 350 A-scans in each B-scan along both the horizontal and the vertical directions. The manufacturer's eye tracking technology was used to reduce motion artifacts. From the volume scans, retina and choroid are automatically segmented into multiple slabs and 2-dimensional angiographic images of each slab are generated. In the current study, angiographic images of the retinal peripapillary capillary (RPC) slab were analyzed. The RPC slab extends from the internal limiting membrane (ILM) to the posterior boundary of the RNFL layer.

All participants underwent a baseline OMAG scan. The cohort of subjects was divided into 2 groups randomly based on the type of repeat scans performed. The non-referenced scan group underwent 2 repeat scans which were not tracked on the baseline scan (Figure 1). The referenced scan group underwent 2 repeat scans which were referenced to the baseline scan using the manufacturer's "track to prior scan" option. When the "track to prior scan" option is selected, the previously saved scanning laser ophthalmoscopy (SLO) fundus image of the baseline scan is overlaid in the scan pattern box over the live SLO fundus image matching for the blood vessel branchings; this allows the repeat scans to be tracked and acquired exactly on the baseline scan (Figure 2). Angiometric software of the Cirrus HD-OCT automatically calculates 2 parameters from the RPC slab along a circular annulus (as shown in Figures 1 and 2). Perfusion density is defined as the total area of perfused vasculature per unit area in the region of measurement. Flux index is defined as the total area of perfused vasculature per unit area in a region of measurement, weighted by the brightness (intensity) of the flow signal. Flux index measures the number of blood cells passing through a retinal vessel cross-sectional area per unit area in the region of measurement. The blood flow signal is normalized to between 0 and 1 (dividing by the full dynamic range of the flow signal). The above OMAG parameters are calculated across the entire annulus (mean measurement) and across 4 sectors of 90 degrees each (temporal, superior, nasal and inferior sectors).

All the examinations for a particular subject were performed on the same day. Image quality was assessed for all OCT and OCTA scans. Poor quality images, defined as those with a signal strength less than 6, and images with motion artifacts and segmentation errors were excluded from the analysis.

STATISTICAL ANALYSIS

To estimate the within-subject standard deviation (S_w) with 15% precision and with 3 repeated measurements per eye, the sample size required in each group for the repeatability analysis was calculated to be 43 eyes.

Intra-session repeatability was assessed by intraclass correlation coefficient (ICC), within-subject standard deviation (S_w), within-subject coefficient of repeatability (CR_w), and within-subject coefficient of variation (CV_w). The S_w was calculated as the square root of the within-subject mean square of error (the unbiased estimator of the component of variance due to random error) in a mixed-effects model.[16] ICC was also calculated from the mixed-effects model.[17] The CR_w was calculated as 2.77 times S_w. The CV_w (100 × S_w/overall mean) was calculated according to the procedure described by Bland and

Altman.[18] Effect of signal strength on the repeatability of OMAG measurements was evaluated using linear mixed effects models for repeated measures.[19] Inter-eye correlation was accounted for in the mixed effects models. Statistical analyses were performed using the Stata version 14.2 (StataCorp, College Station, Tx) statistical software. A p value of ≤0.05 was considered statistically significant.

RESULTS

One hundred and twelve eyes of 64 subjects were initially recruited and all underwent a baseline peripapillary OMAG scan. Sixty-five eyes of 39 subjects underwent 2 repeat non-referenced peripapillary OMAG scans (non-referenced scan group) and 47 eyes of 25 subjects underwent 2 repeat referenced scans (referenced scan group). Of these, 17 eyes with poor quality scans in the non-referenced scan group and 4 eyes with poor quality scans in the referenced scan group were excluded. Final analysis, therefore, included 48 eyes (33 subjects) in the non-referenced scan group and 43 eyes (25 subjects) in the referenced scan group. Table 1 shows the clinical, VF, OCT RNFL thickness and average OMAG measurements of the subjects in the two groups. Distribution of normal, glaucoma suspects and glaucoma eyes were similar between the two groups as was the severity of VF loss. In the non-referenced scan group, the stage of glaucoma was mild (VF mean deviation, MD, better than −6 dB) in 12 eyes (60%), moderate (MD between −6 dB and −12 dB) in 5 (25%) and severe (MD worse than −12 dB) in 3 eyes (15%). In the referenced scan group, the stage of glaucoma was mild in 12 eyes (66.7%), moderate in 5 (27.8%) and severe in 1 eye (5.5%). RNFL thickness and OMAG perfusion densities, however, were lower in referenced scan group compared to non-referenced group, indicating greater severity of structural damage in the eyes within the referenced scan group.

Table 2 shows the repeatability estimates of OMAG measurements in the two scan groups. Repeatability estimates of perfusion density measurements on referenced scans, especially the CRw and ICC, were significantly better than that on non-referenced scans (non-overlapping 95% confidence intervals). Repeatability estimates of flux index measurements on referenced scans were also better than that on non-referenced scans; however, the differences were not statistically significant. Repeatability estimates of perfusion density were better than that of flux index measurements.

CR_w and CV_w of the OMAG measurements on both the referenced and non-referenced scan groups were similar across the control, glaucoma suspect and glaucoma eyes. For example, CR_w, CV_w and ICC of the mean perfusion density in the normal eyes was 1.8% (1.4–2.3), 1.4% (0.7–1.9) and 0.89 (0.80–0.92) respectively on non-referenced scans (13 eyes), and 1.2% (0.9–1.7), 1.0% (0.3–1.4) and 0.93 (0.78–0.98) respectively on referenced scans (9 eyes). CR_w, CV_w and ICC of the mean perfusion density in the suspect and glaucoma eyes was 2.1% (1.8–2.5), 1.8% (0.9–2.4) and 0.88 (0.79–0.93) respectively on non-referenced scans (35 eyes), and 1.4% (1.2–1.7), 1.3% (1.0–1.5) and 0.95 (0.91–0.98) respectively on referenced scans (34 eyes). Repeatability estimates in both the referenced and non-referenced scan groups, also were not associated with the MD or average RNFL thickness ($p>0.05$ for all associations), indicating no association between repeatability and severity of disease.

Table 3 shows the effect of signal strength of the scans on the peripapillary OMAG measurements. Signal strength had similar effects on both non-referenced and referenced scans. Flux index was significantly affected by signal strength with the measurements increasing with increasing signal strength. Perfusion densities of both scans were independent of the signal strength with only the temporal quadrant perfusion density measurement of both non-referenced and referenced scans being negatively associated with signal strength.

DISCUSSION

This study compared the repeatability estimates of peripapillary OMAG measurements between referenced and non-referenced OCTA scans. All estimates were better (less variable) in the referenced scan group compared to the non-referenced scan group. Repeatability of perfusion density were significantly better in the referenced scan group. Repeatability estimates of flux index were also better on referenced scans than non-referenced scans; however, the differences were not statistically significant (overlapping 95% CI). One of the possible reasons for this finding is the wider confidence intervals of the repeatability estimates of flux index measurements (on both referenced and non-referenced scans, as seen in Table 2). This is in turn possibly due to the greater variability of flux index than perfusion density measurements.

There is limited literature on the repeatability estimates of peripapillary OMAG measurements. Using a prototype device and custom scan pattern, Chen et al evaluated the variability of peripapillary OMAG measurements in 4 healthy subjects by acquiring 2 scans within 6 weeks of each other.[20] They found a CV_w of 3.6% for global flux index, 2.8% for temporal, 4.5% for superior, 3.0% for nasal, and 5.5% for inferior sector flux index. For the reproducibility of vessel area density, the CV_w was 2.2% for global vessel area density, and 1.2%, 1.5%, 6.8%, and 1.1% for four sectors, respectively.[20] In contrast, repeatability of peripapillary OCTA measurements using other algorithms (such as split spectrum amplitude decorrelation angiography, SSADA) has been studied extensively. [13, 21], [22, 23] However, all these studies used non-referenced scans to evaluate the repeatability of OCTA measurements. One study found that intra-visit CR_w of peripapillary vessel density (global and sectoral) ranged from 4.1 to 7.1% and CV_w ranged from 2.5% to 6.6%.[21] A few other studies also showed similar repeatability estimates for both intra-visit and inter-visit OCTA measurements.[13], [22, 23] These estimates are similar to the estimates found in the current study on non-referenced scans. One of the above studies compared the variability of OCT and OCTA measurements and found that the CVs of the RNFL thickness measurements were significantly less than that of peripapillary OCTA measurements.[13] The intra-visit and inter-visit CVs of average RNFL thickness was around 1.5%, whereas that of average peripapillary vessel density was close to 4.0% ($P< 0.001$).[13] Results of the current study show that the repeatability estimates of the referenced scans are significantly better than that of the non-referenced scans and also approaches the repeatability estimates of RNFL thickness measurements.

CR_w and CV_w of perfusion density were significantly better than that of the flux index measurements. While perfusion density calculates the average perfusion within a fixed area,

flux index only focuses on the vessel area to minimize bias that less retinal tissue requires less microcirculation. In this way, the flux index measurements are said to better reflect the differences between healthy and diseased retinal tissues.[20] However, the results of the current study shows that perfusion density may be a better parameter than flux index to monitor change over time. Greater variability of average peripapillary normalized flux measurements (ICC of 0.67) compared to peripapillary perfused capillary density (ICC of 0.79) has also been reported using a different OCTA device.[24]

Repeatability of OMAG measurements on both scan groups in the current study were found to be similar among the control subjects, glaucoma suspects and glaucoma patients. Previous studies however have reported higher variability of peripapillary OCTA measurements in glaucoma compared to control subjects.[2, 13, 23] A possible reason for not finding a significant difference in repeatability between the control and glaucoma subjects in the current study is the small sample size. Although the sample size of the current study was adequate to compare the repeatability estimates between the two scan groups, it was possibly small and inadequate to compare the same between the diagnostic groups.

The influence of signal strength of the scan was significantly greater on the flux index compared to the perfusion density measurements. Flux index measurements on both the referenced and non-referenced scans significantly increased with an increase in the signal strength of the scans. As flux index is dependent on the intensity of the flow signal, it is possible that this parameter is affected to a greater extent by the signal strength as compared to perfusion density. In contrast, perfusion density measurements were not affected by the signal strength of the scans, except for the temporal sector perfusion density measurement, which significantly decreased with increase in signal strength. Contrary to the findings of the current study, a study by Lim et al showed a positive correlation between signal strength and peripapillary perfusion density measurements of OMAG.[25] However, this study by Lim et al imaged the optic disc using 3×3 mm scans and the peripapillary region was defined as a circular annulus with an inner circle radius of 1 mm and outer circle radius of 3 mm; this resulted in inclusion of a significant portion of optic nerve head in the peripapillary region.[25] Future studies should validate the results of the current study on the effect of signal strength on OMAG measurements.

The current study compared the repeatability estimates of referenced scans performed in one set of subjects with that of non-referenced scans performed in another set of subjects. Each scan type and its repeatability can be affected by the differences in the inherent characteristics of subjects and it would have been preferable to perform both referenced and non-referenced scans on the same set of subjects. However, the characteristic features of subjects in the two scan groups in the current study were not significantly different and therefore the results are unlikely to be biased. The current study evaluated intra-session repeatability of OMAG measurements. However, it is important to determine inter-session repeatability of measurements while evaluating measurement change over time. Future studies should evaluate inter-session repeatability of OMAG measurements of referenced scans.

In conclusion, the current study showed that the repeatability estimates of OMAG measurements were better on referenced compared to non-referenced scans. Perfusion density measurements had lower variability compared to flux index measurements and were also less affected by signal strength index of the scan. This implies that OCTA-measured perfusion density of referenced scans are preferable for monitoring vascular change in glaucoma.

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SYNOPSIS

Coefficient of repeatability of peripapillary perfusion density measurements (range: 2.0% to 4.1%) on non-referenced scans were significantly higher (higher variability) than that on referenced scans (range: 1.4% to 2.7%).

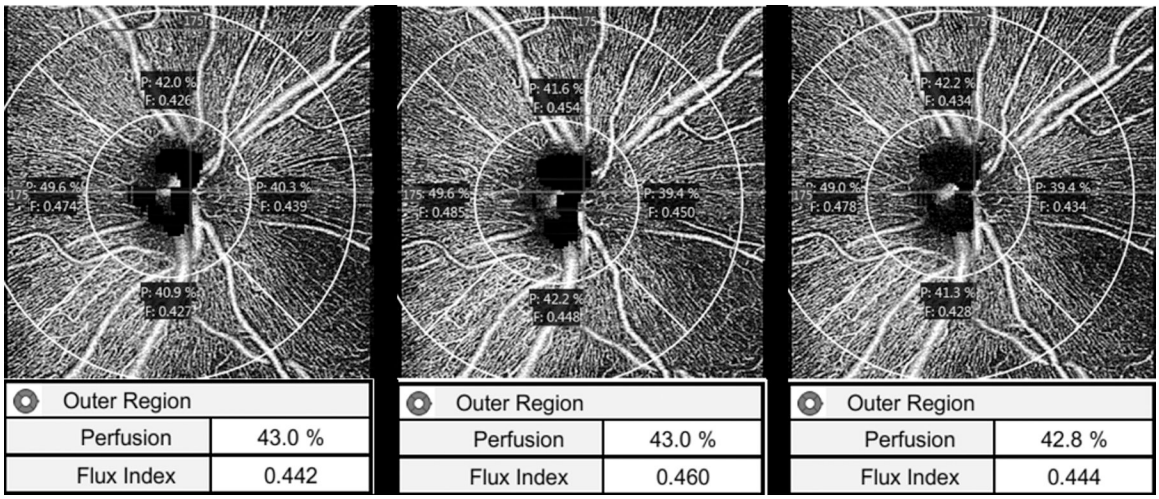

Figure 1.
Example of three repeated non-referenced peripapillary optical microangiography scans of an eye.

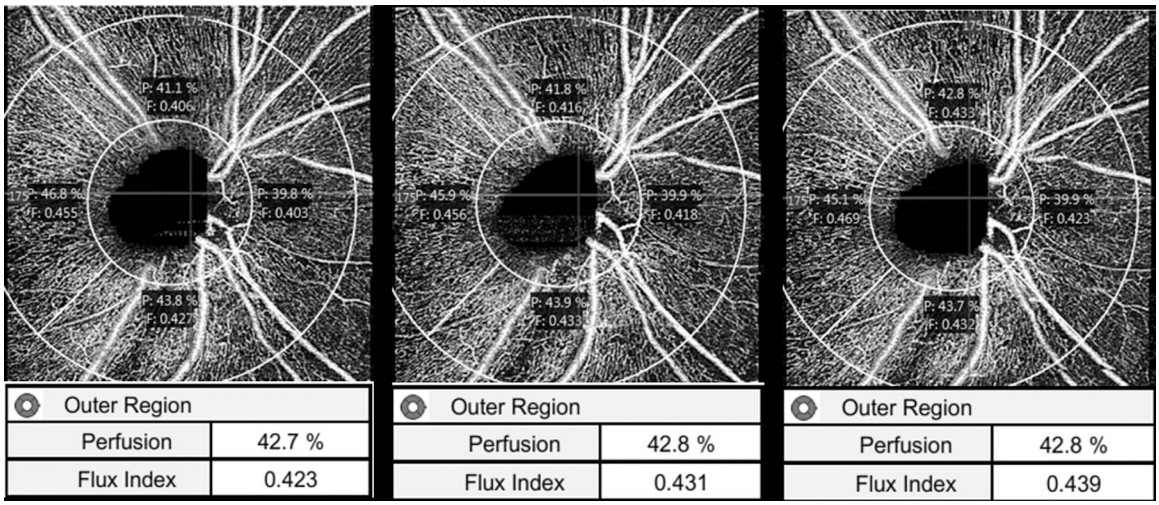

Figure 2.

Example of three repeated referenced peripapillary optical microangiography scans of an eye where the second and third scans are referenced to the first scan using the manufacturer's "track to prior scan" option.

Table 1.

Clinical features, visual field, optical coherence tomography (OCT) and optical microangiography (OMAG) parameters of the participants in the two scan groups. All values represent mean ± standard deviation unless specified.

	Non-referenced scan (48 eyes, 33 subjects)	Referenced scan (43 eyes, 25 patients)	P
Age (years)	52.1±15.3	51.0±15.5	0.80
Gender (male:female)	21:12	18:7	0.50
Sphere (D) *	0 (−1.25, 1.5)	−0.5 (−3.5, 0)	0.02
Cylinder (D) *	−0.5 (−1.25, 0)	−0.5 (−1, 0)	0.40
Pseudophakia (n, %)	4 (8.3%)	4 (9.3%)	0.87
IOP at the scanning visit (mm Hg)	15.4±3.0	16.5±4.4	0.18
Hypertension (yes:no)	9:24	7:18	0.95
Diabetes mellitus (yes:no)	6:27	6:19	0.59
Mean deviation (dB) *	−5.0 (−7.6, −3.0)	−4.8 (−7.8, −4.2)	0.62
Pattern standard deviation (dB) *	3.0 (1.9, 8.1)	4.0 (2.6, 6.8)	0.84
Visual field index (%) *	94 (87, 96)	91 (87, 93)	0.48
Diagnosis			
- Normal	13 (27.1%)	9 (20.9%)	
- Glaucoma Suspect	15 (31.3%)	16 (37.2%)	0.74
- Glaucoma	20 (41.6%)	18 (41.9%)	
	OCT RNFL measurements		
Average Peripapillary RNFL thickness (μm)	82.8 ± 13.1	75.3 ± 16.8	0.02
Temporal RNFL thickness (μm)	59.8 ± 12.9	55.1 ± 12.9	0.09
Superior RNFL thickness (μm)	103.7 ± 20.0	92.2 ± 27.8	0.03
Nasal RNFL thickness (μm)	64.3 ± 11.9	60.3 ± 10.0	0.09
Inferior RNFL thickness (μm)	103.5 ± 22.1	93.8 ± 27.8	0.07
	Average Peripapillary OMAG measurements		
Mean perfusion density (%)	43.1 ± 2.0	42.0 ± 2.4	0.02
Nasal perfusion density (%)	42.4 ± 2.6	41.7 ± 2.8	0.21
Superior perfusion density (%)	41.4 ± 2.8	40.3 ± 2.8	0.07
Temporal perfusion density (%)	46.9 ± 2.5	45.3 ± 2.4	0.003
Inferior perfusion density (%)	41.8 ± 3.5	40.5 ± 4.2	0.10
Average Flux Index (%)	40.0 ± 3.4	39.3 ± 3.8	0.37
Nasal flux index (%)	39.4 ± 3.7	38.8 ± 3.9	0.47
Superior flux index (%)	39.2 ± 3.3	38.9 ± 3.3	0.70
Temporal flux index (%)	41.3 ± 3.9	40.4 ± 4.6	0.29
Inferior flux index (%)	39.5 ± 3.3	38.7 ± 3.9	0.26

D: diopter;

IOP: intraocular pressure;

dB: decibel;

RNFL: retinal nerve fiber layer;

*median and interquartile range.

Table 2.

Repeatability estimates of peripapillary optical microangiography (OMAG) measurements on non-referenced and referenced scans. Figures in the parenthesis represent 95% confidence limits.

OMAG measurement	CRw (%)		CVw (%)		ICC	
	Non-referenced scan	Referenced scan	Non-referenced scan	Referenced scan	Non-referenced scan	Referenced scan
Mean Perfusion density	2.0 (1.8–2.3)	1.4 (1.2–1.6)	1.7 (1.1–2.2)	1.2 (1.0–1.4)	0.88 (0.82–0.92)	0.96 (0.93–0.97)
Nasal	3.4 (2.9–3.9)	2.2 (1.9–2.5)	2.9 (1.9–3.6)	1.8 (1.4–2.2)	0.81 (0.71–0.88)	0.92 (0.88–0.95)
Superior	3.5 (3.1–4.1)	2.2 (1.9–2.6)	3.1 (2.2–3.8)	2.0 (1.4–2.5)	0.82 (0.73–0.88)	0.92 (0.88–0.95)
Temporal	4.1 (3.6–4.7)	2.7 (2.3–3.1)	3.1 (2.1–3.8)	2.1 (1.6–2.6)	0.71 (0.59–0.81)	0.85 (0.77–0.91)
Inferior	2.7 (2.3–3.1)	1.9 (1.7–2.2)	2.3 (1.6–2.8)	1.8 (1.4–2.1)	0.93 (0.88–0.95)	0.97 (0.95–0.98)
Mean flux index	4.4 (3.9–5.1)	3.6 (3.1–4.1)	4.1 (2.4–5.3)	3.3 (2.4–4.1)	0.80 (0.70–0.87)	0.89 (0.83–0.93)
Nasal	5.1 (4.4–5.9)	4.5 (3.9–5.2)	4.8 (2.9–6.1)	4.2 (3.0–5.1)	0.78 (0.68–0.86)	0.84 (0.75–0.90)
Superior	5.5 (4.8–6.3)	3.6 (3.1–4.1)	5.2 (3.4–6.5)	3.4 (2.6–4.1)	0.70 (0.57–0.80)	0.86 (0.78–0.91)
Temporal	5.8 (5.0–6.7)	4.8 (4.2–5.6)	5.2 (3.7–6.3)	4.5 (3.2–5.5)	0.75 (0.64–0.84)	0.87 (0.79–0.92)
Inferior	3.7 (3.2–4.2)	3.4 (2.9–3.9)	3.4 (2.4–4.2)	3.2 (2.6–3.8)	0.86 (0.78–0.91)	0.91 (0.85–0.94)

CRw: coefficient of repeatability; CVw: coefficient of variation; ICC: intraclass correlation coefficient.

Table 3.

Effect of signal strength on the peripapillary optical microangiography (OMAG) measurements.

OMAG measurement	Non-referenced scan		Referenced scan	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Mean Perfusion density (%)	−0.1 (−0.3, 0.2)	0.62	−0.1 (−0.3, 0.1)	0.25
Nasal (%)	−0.3 (−1, 0.1)	0.12	−0.3 (−1, 0.3)	0.07
Superior (%)	0.2 (−0.2, 1)	0.27	0.2 (−0.1, 1)	0.25
Temporal (%)	−1 (−1, −0.1)	0.02	−0.4 (−1, −0.1)	0.01
Inferior (%)	0.3 (−0.1, 1)	0.09	0.2 (−0.1, 1)	0.13
Mean flux index (%)	1.7 (1.2, 2.1)	<0.001	1.5 (1.0, 1.9)	<0.001
Nasal (%)	1.7 (1.2, 2.3)	<0.001	1.6 (1.1, 2.1)	<0.001
Superior (%)	1.9 (1.2, 2.4)	<0.001	1.2 (0.7, 1.6)	<0.001
Temporal (%)	2.1 (1.6, 2.7)	<0.001	1.8 (1.2, 2.3)	<0.001
Inferior (%)	1.1 (0.7, 1.5)	<0.001	1.1 (0.7, 1.5)	<0.001

CI: confidence interval.