The Effect of Medical Lowering of Intraocular Pressure on Peripapillary and Macular Blood Flow as Measured by Optical Coherence Tomography Angiography in Treatment-naive Eyes

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Précis: Reduction of intraocular pressure (IOP) by latanoprost in treatment-naive eyes is significantly correlated to an increase in vessel density (VD) at the optic nerve head (ONH).

Purpose: To evaluate the effect of topical latanoprost on ocular microvascular using optical coherence tomography angiography (OCTA).

Patients and Methods: In this prospective case-control study, 26 eyes from 18 treatment-naive subjects in whom prostaglandin analogue (PGA) latanoprost 0.005% was initiated, were included as cases. In 10 out of the 18 subjects, medication was initiated in only 1 eye; their contralateral untreated eyes were used as controls. OCTA (AngioVue, Optovue Inc., Fremont, CA) was performed at baseline and ≥3 weeks after commencing treatment. Main outcome measures were change in flow area and VD at the ONH, radial peripapillary capillaries (RPC), and macula. Comparison between the 2 visits was performed using a linear mixed model adjusted for intereye correlation and mean ocular perfusion pressure.

Results: IOP decreased by 26.1%±11.3% (P<0.001) in the cases and 0.18%±12.2% (P=0.63) in controls. Significant correlations between change in IOP and change in ONH VD (correlation coefficient [r]=−0.42, P=0.04) and between change in IOP and change in RPC VD (r=−0.48, P=0.02) were observed in the cases, whereas none were observed in the controls. When multiple testing was considered, no significant changes in flow area and VD were observed in cases and controls.

Conclusions: The reduction of IOP by a PGA in treatment-naive eyes was significantly correlated to the increase in ONH VD and RPC VD. This may indicate a mechanism by which IOP reduction modulates the risk of glaucoma progression by improving ocular microperfusion.

Key Words: latanoprost, intraocular pressure, optical coherence tomography angiography, ocular blood flow, glaucoma (J Glaucoma 2021;30:465–472)

The pathogenesis of glaucoma is multifactorial, with vascular dysfunction considered to be one of the factors underlying glaucomatous damage to the optic nerve head.1–5 Findings from several studies lend support to the potential role of ischemic damage in glaucomatous optic neuropathy, either by itself or in conjunction with elevated intraocular pressure (IOP).

The effect of IOP reduction on ocular perfusion pressure and ocular blood flow may be one of the mechanisms by which IOP reduction protects against progression of glaucoma. Previous research on the relationship between IOP and ocular perfusion has shown that reduction of IOP increases the ocular perfusion pressure and consequently improves retrobulbar and optic nerve head (ONH) blood flow.6–11 However, these studies were conducted using older imaging modalities such as fluorescein angiography and color Doppler imaging, which are unsuitable for widespread use to assess microvascular changes because of their invasiveness, low spatial resolution, or poor repeatability.

Optical coherence tomography angiography (OCTA) is a noninvasive imaging modality that allows qualitative and quantitative evaluation of the microvasculature at different layers of the macula, at the ONH, and the peripapillary region.12–13 Reduced perfusion as determined by OCTA parameters at these locations has been observed in varying stages of glaucoma compared with healthy subjects.14 The microvascular changes after surgical IOP reduction have been inconsistent, with some studies showing a postoperative improvement in OCTA parameters while others did not.15–18 Furthermore, there is only 1 case series that evaluated the effect of IOP reduction with topical medication on ocular microvasculature using OCTA.19 Topical IOP-lowering medication is the most common initial treatment option for primary glaucoma, and first-line drugs such as prostaglandins and beta-blockers reduce IOP by up to...
The ability to study the changes in ocular microvasculature induced by IOP-lowering medications may provide a better understanding of the impact of such treatment on glaucoma.

The purpose of this study was to investigate the effect of IOP reduction by latanoprost on ocular microvasculature at the ONH, radial peripapillary capillaries (RPC), and macula in treatment-naïve eyes, using OCTA.

PATIENTS AND METHODS

The study protocol was reviewed and approved by the SingHealth Centralised Institutional Review Board and was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. Subjects were recruited prospectively from the glaucoma clinics of the Singapore National Eye Center. Treatment-naïve subjects diagnosed with primary open-angle glaucoma (POAG), ocular hypertension (OHT), or primary angle closure disease (PACD) requiring the initiation of topical IOP-lowering medication were included. All participants received a prostaglandin analogue (PGA) latanoprost 0.005% (Xalatan; Pfizer Inc., New York) once daily as monotherapy. It was decided to include treatment-naïve patients who were started on the PGA latanoprost 0.005% because it is the most common initial medical therapy in our hospital practice.

POAG was defined by the following criteria: the presence of glaucomatous optic neuropathy (defined as loss of neuroretinal rim with a vertical cup-disc ratio of ≥0.7 or an intereye asymmetry of >0.2, and/or notching) with compatable visual field loss, open angles on gonioscopy, and absence of secondary causes of glaucoma. OHT was defined as IOP >21 mm Hg with normal optic nerve appearance and visual field test. PACD included primary angle closure glaucoma (PACG). PAC was defined as the presence of angle closure where ≥180 degrees of the posterior pigmented trabecular meshwork was not visible on gonioscopy without indentation, normal optic discs, and visual fields, but with elevated IOP (defined as IOP >21 mm Hg) and/or peripheral anterior synechiae. PACG was defined as the presence of angle closure with glaucomatous optic neuropathy with compatible visual field loss. All eyes with PACD had previously undergone laser iridotomy. The contralateral eyes of subjects that required initiation of latanoprost 0.005% because it is the most common initial medical therapy in our hospital practice.

Exclusion criteria were secondary forms of glaucoma, best-corrected visual acuity of <20/40 on a Snellen chart, refractive error >+3.00 D or <-7.00 D, the presence of other coexisting retinal, or neurological diseases that could affect the visual field and the OCTA readings or inability to give informed consent.

Examination Procedures

All participants underwent a standardized ophthalmologic examination that included visual acuity testing, slit-lamp examination, IOP measurement with Goldmann applanation tonometry, and stereoscopic evaluation of the optic disc. Visual field data (Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Dublin, CA, using the Swedish interactive threshold algorithm with a 24-2 test pattern), performed within 6 months of recruitment, were collected from the medical records. Severity of glaucoma was determined from the visual field mean deviation (MD) and was categorized as mild (MD ≥−6 dB), moderate (MD (−6.01 to −12.0 dB), and severe (>−12.01 dB). The procedures done at the baseline visit and at the follow-up visit after a minimum of 3 weeks included measurements of blood pressure and IOP, pupil dilation, and OCTA. Mean ocular perfusion pressure (MOPP) was calculated as two-thirds of the mean arterial pressure minus the IOP, where mean arterial pressure was calculated as two-thirds of the diastolic blood pressure plus one-third of the systolic blood pressure.

OCTA

We used the AngioVue OCTA system (Optovue Inc., Fremont, CA) to quantify the ocular microvascular parameters. The OCTA does not directly measure blood flow; rather vessels are identified on the basis of the presence or absence of detected motion of erythrocytes (ie, flow) that generates a decorrelation signal. En face OCTA images of the ONH, RPC, and macula were generated by maximum decorrelation projection after segmentation and optimized with projection artifact removal. The split-spectrum amplitude-decorrelation angiography algorithm was implemented to optimize the signal-to-noise ratio for flow detection and connectivity of the microvascular networks. Flow area was calculated as the average decorrelation value (correlated with flow velocity) in the selected region and vessel density (VD) was calculated as the percentage area occupied by vessels in the selected region. Each scan was automatically segmented by the AngioVue software (version 2016.2.0.35) to visualize the different perfusion layers. At the macula, the superficial layer was segmented from the inner limiting membrane (ILM) to the inner plexiform layer boundary; the deep layer was segmented from the inner plexiform layer boundary to the outer plexiform layer boundary. The RPC was segmented from the ILM to the posterior retinal nerve fiber layer boundary. The VD and flow area calculations were performed within the macula, ONH, and RPC in cube scans of 4.5×4.5 mm, within a circular region of 3.143 mm² (radius of 1.0 mm) centered on the fovea or the ONH. Separate VD measurements were also done for the automatically determined regions “inside disc” within the anatomic boundary of the disc and in the peripapillary region. At the macula, the whole image, fovea, and parafoveal region were automatically defined and divided into sectors and analyzed per sector (Fig. 1). The foveal avascular zone was outlined by a 0.6-mm diameter circle in which no flow was detected. A trained grader reviewed the quality of the OCTA scans and manually corrected for segmentation accuracy. Scans with poor signal strength (<40) or local artifacts were excluded from the analysis. The reproducibility of the OCTA parameters was assessed in a random subset of 10 eyes by the same grader on separate days.

Statistical Analyses

Statistical analysis was performed using the statistical package IBM SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, NY). First, we compared the baseline characteristics between cases and controls. Then we compared the OCTA parameters, namely flow area and VD at the macular, ONH, and RPC at the follow-up visit with baseline using a linear mixed model adjusted for intereye correlation, signal strength, and MOPP for both cases and controls. We then performed a subgroup analysis in eyes that experienced an IOP reduction of at least 20% from baseline. Correlations were assessed between changes in IOP and MOPP with changes in OCTA parameters for cases (for all cases and for subgroup of at least 20% IOP reduction).
and controls. The covariance type was chosen after considering the smallest values of Akaike’s Information Criterion and Schwarz’s Bayesian Criterion. Correlation of continuous data variables was analyzed using the Pearson correlation test (2-sided). Intraclass correlation coefficient was done to evaluate the intraobserver variability of measurements of OCTA parameters. Appropriate Bonferroni correction was applied to correct for number of parameters studied at the ONH, RPC, and macula, respectively.

RESULTS

Of the 36 eyes from 20 participants that were included, medication was required for 26 eyes (18 patients) including 15 POAG, 3 OHT, 8 PACD), with the remaining 10 eyes not requiring medication included as controls. Seven participants were excluded because they did not complete the follow-up and 4 eyes were excluded because of poor signal strength of the OCTA images. Diabetes was present in 8 (40.0%) and hypertension in 13 (65.0%) subjects. Of the 26 treated eyes, 21 (80.8%) were categorized as having mild glaucoma with a mean visual field MD of (−3.01 ± 1.75) and 5 eyes (19.8%) as moderate-severe glaucoma with a mean MD of −18.25 ± 7.66.

The mean age of the 18 subjects was 60.7 ± 13.7 years (range, 29 to 77 y) and 11 (61.1%) were male individuals. The mean duration between the baseline visit and follow-up visit was 64.6 ± 25.2 days (range, 22 to 114 d). Overall, IOP decreased by 26.1% ± 11.3% from the pretreatment mean of 20.2 ± 4.5 to 14.6 ± 2.5 mm Hg (P < 0.001) in the cases, and 0.18% ± 12.2% (16.4 to 16.1 mm Hg; P = 0.63) in controls. In 19 of 26 eyes (73%), we observed a reduction in IOP of at least 20%.

Table 1 shows the comparison of baseline OCTA parameters adjusted for IOP between cases and controls. Flow area and VD at the ONH, RPC, and macula were lower in cases compared with controls; however, no significant differences were observed when multiple testing was considered. Details of the comparison of OCTA parameters

FIGURE 1. En face optical coherence tomography angiography images of optic disc (A), peripapillary ellipse defining region for measurements (B), macula showing region of flow area measurements (C) and sectoral subdivision of parafoveal area (D).
between follow-up and baseline visit for the cases and controls are shown in Table 2. In the cases, we did not find any significant changes in flow area or VD at the ONH or RPC. There were no significant changes in macular VD. However, we observed a modest increase in macular deep retina flow area from 0.81 ± 0.05 to 0.93 ± 0.05 mm² (P = 0.02). In the control eyes, we observed no significant differences in any of the parameters.

Table 3 demonstrates the correlations of change in IOP and change in MOPP with the changes in OCTA parameters in the cases and controls. In the cases, there were significant positive correlations between change in IOP and change in ONH VD (correlation coefficient \( r = -0.42, P = 0.04 \)), change in IOP and change in RPC inside disc VD (\( r = -0.48, P = 0.02 \)), and modest correlations between change in RPC flow with both change in IOP (\( P = 0.05 \)) and change in MOPP (\( P = 0.05 \)). No significant correlations were noted in the controls. We found no correlation between treatment duration and changes in any of the OCTA parameters, or between baseline IOP and baseline OCTA parameters (data not shown).

We next performed a subgroup analysis in the 19 eyes that experienced a reduction in IOP of at least 20% (Table 4). The mean reduction in IOP was 30.1% from 22.1 ± 4.3 to 15.5 ± 1.7 mm Hg (P < 0.001). Although we observed an increase in macular deep retina flow area from 0.78 ± 0.07 to 0.93 ± 0.07 mm² (\( P = 0.02 \)) and also an increase in deep retina parafoveal VD (\( P = 0.04 \)), when multiple testing was considered, the observations were not significant. Further evaluation of the parafoveal sectors of these eyes with at least 20% IOP reduction showed an increase in VD in all sectors (Table 4), but the changes did not reach statistical significance (all \( P \) values > 0.008).

The intraobserver reproducibility of the OCTA measurements was excellent with the intraclass correlation coefficient ranging from 0.90 to 1.00.

**DISCUSSION**

In this study, we investigated the effect of IOP reduction by latanoprost on ocular microvasculature at the ONH, RPC, and macula in treatment-naïve eyes, using OCTA. Our study showed that a modest change in IOP (IOP reduction) was significantly correlated with the change in VD (increase in VD) at the ONH and RPC observed 3 or more weeks after initiation of treatment, and detectable by OCTA imaging. Whereas we observed an increase in VD in sectors of the deep parafoveal retina in eyes with at least 20% IOP reduction, however, the observations were not significant when multiple testing was considered.

The only other study that investigated the effect of medical IOP-lowering therapy on ocular perfusion using OCTA was by Holló, who described a case series of 6 eyes of young patients with a high baseline IOP ranging from 35 to 42 mm Hg. After medical IOP lowering, all eyes showed > 50% decrease in IOP and an increased peripapillary capillary VD, but perfusion at the macula was not evaluated. Our study did not replicate these results, which could be explained by several factors. In Holló’s case series, the mean baseline IOP was higher than in our population. Consequently, the IOP reduction was also larger in his subjects. It was therefore possible that microvascular impairment may have not occurred in our subjects because of the relatively low baseline IOP, or, changes may have been too small to be detected because of the smaller magnitude of IOP reduction. The medical therapy given in Holló’s case series also varied between subjects and was different from our study, and may have led to different direct pharmacological vasomotor effects.

The reproducibility of OCTA measurements in our patients is similar to published data on healthy and glaucomatous eyes, which has shown good reproducibility for the retinal and ONH microvasculature measurements. It is unknown whether the modest improvement that we
This corroborates earlier findings using Doppler OCT and laser Doppler velocimetry, indicating the presence of an active process of vascular autoregulation to maintain ocular blood flow during increase in IOP and reduced MOPP. 

An improvement of ocular microvasculature is proposed by several authors to influence the rate of glaucoma progression, although convincing evidence for this hypothesis is currently unavailable. Further research is warranted to explore the impact of IOP reduction on the different microvascular layers of the eye. Interestingly, in a retrospective study on the relationship between retinal VD and glaucoma progression, Jeon et al. found that patients with progressive glaucoma had lower deep macular VD compared with nonprogressors.

Several studies have investigated the effect of surgical IOP lowering on ocular microvasculature using OCTA, although most of them focused entirely on the ONH and peripapillary region. Kim et al. studied the peripapillary region. Similarly, a change in perfusion at the peripapillary region. This might be explained by the fact that their population had a comparable baseline IOP of 23.1 mm Hg as in our study, which might not have been high enough to show a microvascular change in the peripapillary region. Similarly,

| Cases | Controls |
|-------|----------|
| Visit 1 | Visit 2 | Adjusted Mean Difference* | P* | Visit 1 | Visit 2 | Adjusted Mean Difference* | P* |
| ONH† | ONH flow area (mm²) | 1.34 (0.06) | 1.38 (0.06) | −0.04 (−0.05 to 0.08) | 0.51 | 1.51 (0.05) | 1.52 (0.05) | −0.02 (−0.13 to 0.09) | 0.66 |
| ONH whole VD (%) | 49.23 (1.10) | 49.25 (1.07) | −0.02 (−1.72 to 1.69) | 0.98 | 52.26 (1.04) | 51.89 (0.99) | 0.37 (−2.31 to 3.04) | 0.75 |
| ONH inside disc VD (%) | 45.38 (1.65) | 44.50 (2.08) | 0.86 (−1.35 to 3.12) | 0.44 | 47.65 (1.37) | 49.13 (1.33) | −1.48 (−4.10 to 1.14) | 0.23 |
| ONH peripapillary VD (%) | 52.30 (1.34) | 52.76 (1.29) | −0.46 (−2.56 to 1.65) | 0.66 | 57.17 (1.03) | 56.00 (0.98) | 1.17 (−1.78 to 4.14) | 0.38 |
| RPC‡ | RPC flow area (mm²) | 1.15 (0.08) | 1.05 (0.08) | 0.10 (−0.02 to 0.22) | 0.10 | 1.11 (0.11) | 1.10 (0.11) | 0.01 (−0.07 to 0.09) | 0.69 |
| RPC whole VD (%) | 47.33 (1.34) | 47.15 (1.32) | 0.18 (−1.27 to 1.63) | 0.81 | 50.53 (1.21) | 48.77 (1.17) | 1.76 (−0.98 to 4.50) | 0.16 |
| RPC inside disc VD (%) | 31.42 (2.64) | 27.29 (2.51) | 4.13 (−0.62 to 8.87) | 0.09 | 30.67 (3.08) | 31.04 (3.02) | −0.37 (−5.00 to 4.26) | 0.86 |
| RPC peripapillary VD (%) | 53.45 (1.50) | 54.57 (1.44) | −1.11 (−3.53 to 1.30) | 0.36 | 59.77 (1.43) | 58.15 (1.38) | 1.62 (−1.24 to 4.48) | 0.21 |
| Retina (Macula)‡ | Superficial retina flow area (mm²) | 1.11 (0.03) | 1.12 (0.03) | −0.03 (−0.08 to 0.03) | 0.32 | 1.10 (0.06) | 1.11 (0.06) | −0.007 (−0.17 to 0.16) | 0.92 |
| Deep retina flow area (mm²) | 0.81 (0.05) | 0.93 (0.05) | −0.12 (−0.22 to −0.02) | 0.02 | 0.95 (0.10) | 0.83 (0.09) | 0.12 (−0.17 to 0.40) | 0.28 |
| Superficial whole VD (%) | 42.57 (0.91) | 41.91 (0.87) | 0.67 (−0.69 to 2.04) | 0.32 | 41.00 (0.84) | 41.97 (0.47) | −0.99 (−3.43 to 1.44) | 0.41 |
| Superficial fovea VD (%) | 28.76 (1.37) | 27.86 (0.56) | 0.90 (−4.06 to 5.86) | 0.65 | 23.59 (1.70) | 24.54 (1.56) | −0.96 (−4.95 to 3.04) | 0.58 |
| Superficial parafovea VD (%) | 45.89 (1.36) | 45.30 (0.65) | 0.59 (−1.30 to 2.49) | 0.51 | 44.20 (1.37) | 45.43 (1.25) | −1.23 (−4.5 to 2.05) | 0.40 |
| Deep whole VD (%) | 48.73 (0.92) | 48.28 (0.86) | 0.46 (−1.40 to 2.31) | 0.61 | 48.02 (1.07) | 48.82 (0.99) | −0.80 (−2.91 to 1.31) | 0.45 |
| Deep fovea VD (%) | 28.52 (2.35) | 25.24 (2.15) | 3.28 (−2.31 to 8.87) | 0.24 | 22.59 (2.20) | 22.44 (1.97) | 0.15 (−6.58 to 6.89) | 0.95 |
| Deep retina parafovea VD (%) | 54.05 (1.15) | 54.51 (1.09) | −0.46 (−2.50 to 1.58) | 0.65 | 54.91 (1.04) | 53.95 (0.93) | 0.96 (−2.95 to 4.87) | 0.57 |

*Linear mixed model: adjusted for intereye correlation, MOPP, and signal strength.
†P value threshold of 0.01 to be considered statistically significant.
‡P value threshold of 0.006 to be considered statistically significant.
MOPP indicates mean ocular perfusion pressure; ONH, optic nerve head; RPC, retinal peripapillary capillary; SE, standard error; VD, vessel density.

observed in some of the OCTA parameters occurred by reperfusion or possibly because of revascularization. Importantly, as baseline IOP was not correlated with baseline VD or flow area, it may suggest that the changes in OCTA parameters be ascribed to changes affected by IOP reduction. Studies using laser Doppler flowmetry have shown that ocular perfusion can be sustained during acutely induced moderate IOP elevation and reduced MOPP. In a recent study using Doppler OCT, retinal blood flow in response to an experimental decrease in MOPP induced by stepwise elevation of IOP was investigated. The authors found that the retinal blood flow was autoregulated until the MOPP was reduced by −21 mm Hg; and it only started to decrease significantly when the MOPP was reduced by 30 mm Hg. Furthermore, another study found that the ONH and macular VD measured by OCTA did not show changes in eyes with an acute IOP elevation of 10 to 15 mm Hg after a dark room test. This corroborates earlier findings using Doppler OCT and laser Doppler velocimetry, indicating the presence of an active process of vascular autoregulation to maintain ocular blood flow during increase in IOP and reduced MOPP.
Zéboulon et al\textsuperscript{16} studied both the peripapillary and macular VD using OCTA in patients with glaucoma after trabeculectomy. Their participants had a relatively low baseline IOP of 23.7 mm Hg, and a limited change in peripapillary and macular VD was observed after 1 month. In contrast, In et al\textsuperscript{15} found a significant increase in the peripapillary VD after trabeculectomy, after lowering the mean IOP by 59.1\% from 30.92 mm Hg at baseline, to 12.64 mm Hg. The magnitude of the increase in peripapillary VD was significantly associated with higher baseline IOP and larger IOP reduction. Interestingly, the significant increase in peripapillary VD was only detected at the postoperative month 3 visit.

### TABLE 3. Comparison of the OCTA Parameters at the ONH, RPCs, and Macular Region at Baseline and Follow-up Visits in Cases Which Demonstrated at Least 20\% IOP Reduction Compared With Baseline

| ONH | Visit 1 Mean (SE) | Visit 2 Mean (SE) | Adjusted Mean Difference* | P* |
|-----|------------------|------------------|----------------------------|-----|
| ONH flow area (mm\(^2\)) | 1.38 (0.07) | 1.41 (0.07) | −0.03 (−0.16 to 0.12) | 0.71 |
| ONH Whole VD (%) | 50.16 (1.31) | 50.37 (1.31) | −0.20 (−2.37 to 1.96) | 0.85 |
| ONH inside disc VD (%) | 45.52 (2.91) | 44.76 (2.82) | 0.76 (−4.23 to 5.75) | 0.75 |
| ONH peripapillary VD (%) | 52.89 (1.62) | 53.06 (1.56) | −0.14 (−2.58 to 2.24) | 0.88 |

| RPC | Visit 1 Mean (SE) | Visit 2 Mean (SE) | Adjusted Mean Difference* | P* |
|-----|------------------|------------------|----------------------------|-----|
| RPC flow area (mm\(^2\)) | 1.18 (0.09) | 1.09 (0.08) | 0.09 (−0.07 to 0.26) | 0.24 |
| RPC whole VD (%) | 48.34 (1.59) | 47.59 (1.57) | 0.74 (−1.59 to 3.08) | 0.51 |
| RPC inside disc VD (%) | 30.86 (3.86) | 29.83 (3.75) | 1.03 (−5.38 to 7.43) | 0.74 |
| RPC peripapillary VD (%) | 54.39 (1.63) | 54.09 (1.60) | −0.30 (−2.00 to 2.61) | 0.78 |

| Retina (macula\(\dagger\)) | Visit 1 Mean (SE) | Visit 2 Mean (SE) | Adjusted Mean Difference* | P* |
|-----------------------------|------------------|------------------|----------------------------|-----|
| Superficial retina flow area (mm\(^2\)) | 1.09 (0.03) | 1.14 (0.03) | −0.05 (−0.11 to 0.01) | 0.12 |
| Deep retina flow area (mm\(^2\)) | 0.78 (0.07) | 0.93 (0.07) | −0.14 (−0.26 to −0.03) | 0.02 |
| Superficial whole VD (%) | 41.54 (1.04) | 41.36 (0.66) | 0.18 (−0.65 to 1.02) | 0.66 |
| Superficial fovea VD (%) | 29.15 (1.71) | 27.41 (0.76) | 1.74 (−1.42 to 4.72) | 0.25 |
| Superficial parafovea VD (%) | 44.75 (0.95) | 45.78 (0.91) | −1.02 (−2.45 to 0.41) | 0.15 |
| Deep whole VD (%) | 48.10 (1.12) | 48.43 (1.04) | −0.34 (−2.73 to 2.06) | 0.77 |
| Deep fovea VD (%) | 30.17 (3.22) | 25.93 (3.02) | 4.24 (−1.92 to 10.41) | 0.17 |
| Deep retina parafovea VD (%) | 52.64 (1.01) | 54.87 (0.94) | −2.23 (−4.36 to 0.11) | 0.04 |

| Sectoral distribution of the deep retina parafovea VD\(\ddagger\) | Visit 1 Mean (SE) | Visit 2 Mean (SE) | Adjusted Mean Difference* | P* |
|-----------------------------|------------------|------------------|----------------------------|-----|
| Superior hemi | 53.18 (1.20) | 55.74 (1.13) | −2.56 (−4.89 to −0.22) | 0.03 |
| Inferior hemi | 52.06 (0.98) | 53.73 (0.88) | −1.67 (−4.19 to 0.86) | 0.18 |
| Temporal | 53.18 (1.05) | 54.05 (0.97) | −0.86 (−3.08 to 1.36) | 0.42 |
| Superior | 53.00 (1.06) | 56.81 (0.95) | −3.80 (−7.24 to −0.307) | 0.03 |
| Nasal | 52.52 (1.31) | 53.56 (1.18) | −1.04 (−5.03 to 2.94) | 0.58 |
| Inferior | 51.82 (1.48) | 53.82 (1.36) | −2.00 (−5.65 to 1.66) | 0.26 |

* Linear Mixed Model: adjusted for intereye correlation, MOPP, and signal strength.
† P value threshold of 0.01 to be considered statistically significant.
‡ P value threshold of 0.006 to be considered statistically significant.
§ P value threshold of 0.008 to be considered statistically significant.
IOP indicates intraocular pressure; MOPP, mean ocular perfusion pressure; OCTA, optical coherence tomography angiography; ONH, optic nerve head; RPC, retinal peripapillary capillary; SE, standard error; VD, vessel density.
even though the magnitude of IOP reduction at month 3 was similar to the postoperative week 1 and month 1 visit. This suggests that changes in peripapillary VD may only be detectable with a longer follow-up period. As our follow-up duration had a mean of 64.6 days after initiation of latanoprost, it is possible that the changes in microvasculature may not have yet occurred. In another study of eyes that underwent trabeculectomy for POAG, Shin et al.38 observed no significant changes in vascular density of the RPC, but observed a thickening of the retinal nerve fiber layer. However, interpretation of these results is limited by the heterogeneity of the treatments included.

It is important to comprehend the parameters that are measured by the OCTA. The flow area and VD are inferred by the detection of moving erythrocytes through the lumen of the vessels. This approximated quantification of flow area and VD by the OCTA software is not a measurement of true perfusion and can differ from the anatomic parameters through several confounders and artifacts, such as the changes in vessel diameter and vessel wall thickness. The velocity in the ocular capillaries may also be too low, such that it impedes the detection of decorrelation signals.

One of the limitations of our study was the relatively small and heterogenous sample. However, we have tried to minimize the diversity by including only treatment-naive subjects in whom treatment was initiated with latanoprost 0.005% monotherapy. The generalizability of our findings to all glaucoma patients is limited, and separate studies in POAG and PACG should be performed. Second, the low baseline IOP may not have affected impairment of ocular microperfusion or the changes may not have been detected because of the relatively small change in IOP. Nonetheless, we were still able to observe significant correlations in ocular microvasculature using OCTA after IOP reduction despite the relatively low baseline IOP levels. Third, the brevity and varying range of the follow-up duration may have diluted the impact of our findings. The reason for the wide follow-up duration is that in our clinical practice, the follow-up visit after initiation of glaucoma medication is usually 3 to 12 weeks, depending upon the baseline IOP and disease severity. As we have seen in other studies, ocular perfusion might change over time.15 Also, 8 out of 10 eyes in our relatively small control group were contralateral eyes that did not receive medication. Although this limits heterogeneity because of any systemic differences between cases and controls, some topical medications are shown to decrease IOP in the contralateral eye that does not receive treatment,40,41 which could have biased our results toward less significance. However, it is likely that the medications contributed minimal effect to our controls, as we observed no significant changes in the IOP of the control eyes. Ideally, the presence of a larger control group is preferred with no overlap in participants between cases and controls. Finally, although we found an increase in the VD at the ONH and parafoveal retina in the cases but not controls, however, the findings were not statistically significant after correction for multiple comparisons.

In conclusion, even with a modest IOP reduction by latanoprost in a treatment-naive population with a moderately elevated baseline IOP, there was a significant correlation between change in IOP and change in VD at the ONH and RPC. However, more research is needed with longer follow-up to further reveal the intrinsic multifactorial influences of ocular perfusion in glaucoma and how this ultimately influences glaucoma progression in the long term.

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