Glaucoma

Microvasculature Recovery Detected Using Optical Coherence Tomography Angiography and the Rate of Visual Field Progression After Glaucoma Surgery

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PURPOSE. We evaluated microvascular changes using optical coherence tomography angiography (OCT-A) in glaucoma patients who underwent glaucoma surgery.

METHODS. The macula and optic nerve head were imaged using an OCT-A device at one day before surgery and at one week, one month, three months, and six months after surgery. Measurements of vessel density (VD) were made in the intradisc region and macula, and the area of the foveal avascular zone (FAZ) was measured in both superficial and deep vascular layers. A mean deviation (MD) slope value of < -1.0 decibel/y was considered to be indicative of VF progression.

RESULTS. A significant increase in VD was observed postoperatively in the deep vascular layer of the intradisc area ($P < 0.001$), and a significant decrease in the FAZ area was evident in the deep vascular layer ($P = 0.018$). An increase in the intradisc deep VD ($17.48\% \pm 5.63\%$) was statistically significant in glaucoma eyes without progression, compared with those with progression ($-1.27\% \pm 2.19\%$). Worse preoperative MD of the VF ($P = 0.006$), lower preoperative intradisc VD ($P < 0.001$), and fewer changes in the intradisc deep VD after surgery ($P < 0.001$) were significantly associated with MD slope.

CONCLUSIONS. We found deep VD changes in the laminar region of the optic nerve head and the macular area at up to postoperative one month after glaucoma surgery. An increase in the deep VD in the laminar region was beneficial to VF progression in glaucoma patients after surgery.

Keywords: glaucoma, glaucoma surgery, optical coherence tomography angiography

Elevated intraocular pressure (IOP) is the most important factor contributing to glaucoma development and progression. It is well characterized in imaging studies that an elevated IOP may lead to compression and displacement of the lamina cribrosa (LC), resulting in axonal damage underlying the glaucomatous process.[1] Changes in the LC may induce kinking or distortion of the axons that pass through the laminar pores, leading to axoplasmic blockages that damage the retinal ganglion cells (RGCs).[2] These effects may further lead to compression of the capillaries that pass through the LC, thus resulting in ischemic insult to the axons. Therefore elevated IOP may induce both structural and vascular changes that contribute to glaucoma.

Previous studies using fluorescein angiography or indocyanine green angiography have shown that elevated IOP disturbs blood flow around the optic nerve head (ONH).[3–7] With the advent of optical coherence tomography angiography (OCT-A), we can measure the vascular density both qualitatively and quantitatively, as microvascular data, to facilitate the evaluation of the perfusion status of the various retinal layers and ONH tissues. Specifically, OCT-A images typically show improvement in the peripapillary and macular microcirculation with IOP reduction after glaucoma surgery[8–13]; however, the specific changes in the microcirculation and the effects on glaucoma progression have not been resolved to date. Investigating the role of microvascular changes after IOP reduction is important to better understand the glaucomatous process for determining treatment options.

In this study, we evaluated microvascular changes using OCT-A in glaucoma patients who underwent glaucoma surgery. Serial observations of vessel density (VD) status in the macula and the ONH were performed in an attempt to clarify the relationship between

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VD and visual field (VF) progression after glaucoma surgery.

Methods

Subjects

We prospectively recruited primary open-angle glaucoma (POAG) patients who were scheduled for glaucoma surgery at Seoul St. Mary's Hospital between March 2017 and May 2020 because of uncontrolled IOP. The work was approved by the Institutional Review Board of Seoul St. Mary's Hospital, and the study adhered to all relevant tenets of the Declaration of Helsinki. We enrolled all consecutive eligible patients who were willing to participate, and all gave written informed consent.

All POAG patients enrolled in the study underwent a complete ophthalmic examination, including a review of medical history, measurement of best-corrected visual acuity, refraction assessment, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, measurement of the central corneal thickness via ultrasound pachymetry (Tomey Corp., Nagoya, Japan), measurement of axial length with ocular biometry (IOL Master; Carl Zeiss Meditec, Dublin, CA, USA), dilated stereoscopic examination of the optic disc, red-free fundus photography (Canon, Tokyo, Japan), Cirrus OCT (Carl Zeiss Meditec), Humphrey VF examination using the Swedish interactive threshold Standard 24-2 algorithm (Carl Zeiss Meditec), and OCT-A imaging (DRI OCT Triton; Topcon, Tokyo, Japan).

POAG was defined by the presence of a glaucomatous optic disc (exhibiting diffuse or localized rim thinning, a notch in the rim, or a vertical cup-to-disc ratio of ≥ 0.2 with respect to the other eye); a VF finding consistent with glaucoma (a cluster of ≥ 3 non-edge points in pattern deviation plots with a probability of $<5\%$ of the normal population, with one of these points having a probability of $<1\%$); a pattern standard deviation (PSD) with a *P* value $<5\%$ or a glaucoma hemifield test result consistently outside the normal limits on two preoperative VF examinations as confirmed by two glaucoma specialists (H.Y.P. and C.K.P.); and an open angle evident on gonioscopy.

The exclusion criteria were a best-corrected visual acuity worse than 20/40, a spherical refraction of <-8.0 diopters (D) or $>+3.0$ D, a cylinder correction of <-3.0 D or $>+3.0$ D, a history of any retinal disease, a history of eye trauma or surgery with the exception of uncomplicated cataract surgery, any optic nerve disease apart from glaucoma, and a history of systemic or neurological disease that might affect the VF. If both eyes of an enrolled patient met all inclusion and exclusion criteria, one eye was randomly chosen for study.

The indications for glaucoma surgery were based on the progression of glaucomatous damage (VF, optic disc, or both) and elevated IOP despite maximum tolerated medical therapy. All ocular hypotensive medications were continued up to the time of surgery. Cataract grading was performed by the same ophthalmologist using the LOCS III grading system during preoperative and postoperative follow-up.[14] The presence of postoperative complication was recorded, such as hypotony (defined as IOP less than 6 mm Hg during the postoperative one-month period), shallow anterior chamber, choroidal detach, and the presence of hypertensive phase (defined as IOP > 21 mm Hg during the first postoperative three-month period). Patients with hypotony, maculopathy, or disc edema were excluded. Additional exclusion criteria were progression of cataract defined as increase in LOCS grading by more than one scale or who needed cataract surgery after surgery, any postoperative complication that required further intervention, and eyes that needed a second procedure or surgery. The IOP measurement and OCT-A images of the macula and ONH were evaluated at one day before surgery and at one week, one month, three months, and six months after surgery. Percent IOP reduction was calculated from the amount of IOP change at postoperative one day to preoperative IOP divided by preoperative IOP value. Standard deviation of postoperative IOP was calculated as the standard deviation of IOP values at postoperative one week, one month, three months, and six months.

Optical Coherence Tomography Angiography and Determination of Microvascular Changes

The macula and ONH region were imaged using a commercial, swept-source OCT-A device (DRI OCT Triton; Topcon Corp.). The central wavelength was 1050 nm, the acquisition speed was 100,000 A-scans/s, and the axial and transversal resolutions were 7 and 20 µm, respectively. Cubes 4.5×4.5 mm^2 in size were scanned; each cube consisted of 320 clusters of four repeated B-scans centered on the fovea and optic disc. The instrument uses an active eye tracker that follows eye movement, such that motion artifacts are reduced during image acquisition. Only clear images with quality scores >30 that did not exhibit blurring attributable to motion or blinking were analyzed. The scanned images were extracted from the OCT-A device and imported into ImageJ software (http://rsb.info.nih.gov/ij/index.html; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA).

VD measurements were made in the intradisc area, within the region of β-zone peripapillary atrophy (PPA), as well as in the macular region. Details are in our previous studies.[12–15] The area of the foveal avascular zone (FAZ) was measured. In the peripapillary region, automated layer segmentation was performed. For the imaging of superficial peripapillary microvasculature, the radial peripapillary capillary segment extending from the internal limiting membrane (ILM) to the retinal nerve fiber layer (RNFL) was analyzed. For the imaging of deep peripapillary microvasculature, the embedded segmentation program demarcated the boundary line from 130 µm below the ILM to 390 µm below the basement membrane, including the inner nuclear layer (INL), outer plexiform layer, outer nuclear layer, and choroid. To measure the VD in the intradisc and β-zone PPA regions, the optic disc (Fig. 1A, yellow dotted line) and β-zone PPA region (Fig. 1A, green dashed line) were delineated from the disc photograph and superimposed onto the OCT-A image. The VD within the optic disc and β-zone PPA region was measured from images of both superficial (Fig. 1B) and deep (Fig. 1C) vascular layers. The VD in the β-zone PPA region was measured only in eyes with β-zone PPA. In the macular region, automated layer segmentation was performed for the superficial vascular plexus (2.6 µm below the ILM to 15.6 µm below the junction between the inner plexiform layer [IPL] and INL) and deep vascular plexus (15.6 µm below the IPL/INL to 70.2 µm below the IPL/INL). En-face projections of volumetric scans allow for the visualization of structural and vascular details within segmented retinal layer
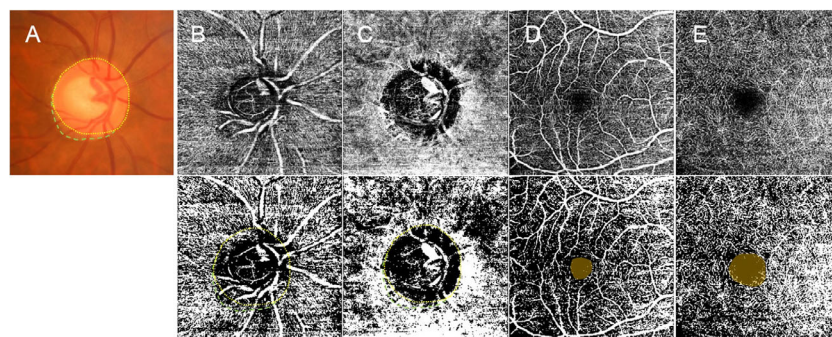
Figure 1. Measurement of VD using OCT-A. **(A)** The optic disc (*yellow dotted line*) and β-zone PPA (*green dash line*) area were delineated from the disc photograph and superimposed on the converted OCT-A images (below **B** and **C**); **(B)** superficial vascular map; **(C)** deep vascular map. The FAZ area was measured by manually tracing the FAZ (*orange shaded area*) on the converted OCT-A images (below **D** and **E**) and automatically calculating the pixel area using Image J software. **(D)** Superficial vascular map; **(E)** deep vascular map. VD within the optic disc (intradisc VD) and the β-zone PPA region, macular VD from the whole macular map, and the FAZ area were measured from both the superficial and deep vascular layers at each preoperative and postoperative periods.

boundaries. Macular superficial and deep VD were measured from images of both superficial (Fig. 1D) and deep (Fig. 1E) vascular layers. The FAZ area was measured from images of both macular superficial and deep layers. The FAZ contours were manually traced and the pixel area was automatically calculated using Image J software. An 8-bit binary slab was then created using the mean threshold algorithm in ImageJ, which automatically computes the threshold value as the mean of the local grayscale distribution (each converted image below Figs. 1B–E). After assigning white pixels as vessels and black pixels as the background, the VD was defined as the percentage of vessel pixels relative to the total area. Two independent observers (H.Y.P and S.J.) blinded to the clinical data independently measured VD parameters of en-face OCT-A images and then averaged the data, which were used in the final analyses.

Determination of VF progression

Patients with two reliable VF tests that was performed within a month period preoperatively and reliable follow-up VF tests at one month, three months, and six months after surgery (for a total of five tests) were included in the analysis. The definition of a reliable VF test was fixation losses <20%, false-positive responses <15%, and false-negative responses <15%. The same criteria were used to determine the reliability of baseline VF tests before and after surgery. VF progression was determined using linear regression analysis of the mean deviation (MD) values from the five VF tests. The MD progression rate is expressed as the change in decibels (dB) per year. An MD slope <-1.0 dB/y was considered to be indicative of VF progression.

Statistical Analysis

The interobserver reproducibility was evaluated by having two observers (H.Y.P and S.J.) measure VD and the FAZ area in 30 randomly selected eyes, to calculate the intraclass correlation coefficients (ICCs) and their confidence intervals (CIs). We used Student's *t*-test and the χ^2 test to compare continuous and categorical variables, respectively. A paired *t*-test was used to compare variables before and after surgery. Significant changes in the measured VD parameters were defined as those exceeding the 95% Bland–Altman limits of agreement. Univariate and multivariate linear regression analyses were used to identify factors asso-

ciated with VF progression. The dependent variable was the value of the MD slope, and the independent variables were age, sex, previous glaucoma surgery, axial length, central corneal thickness, preoperative and postoperative IOP, average RNFL and macular ganglion cell (GC)/IPL thickness, MD and PSD of the VF, preoperative VD parameters and the FAZ area, changes in VD parameters and the FAZ area, OCT-A image quality score, and follow-up period. A *P* value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 102 eyes of 102 glaucoma patients who underwent glaucoma surgery met the inclusion criteria and underwent serial OCT-A imaging. Of these, 14 (13.7%) were excluded from further analysis because the OCT-A images were of

TABLE 1. Preoperative Characteristics and Parameters of OCT-A of 88 Eyes of 88 Glaucoma Patients Who Underwent Glaucoma Surgery

Variables	Description
Age, year	57.14 ± 15.76
Female	26 (29.5%)
Previous glaucoma surgery	10 (11.4%)
Type of glaucoma surgery	
Trabeculectomy	62 (70.5%)
Express shunt	14 (15.9%)
Ahmed drainage device	12 (13.6%)
Type of medications	
β-blocker	84 (95.5%)
α-agonist	84 (92.0%)
Carbonic anhydrase inhibitors	83 (94.3%)
Prostaglandin	83 (94.3%)
Spherical equivalent, diopters	−2.07 ± 3.04
Axial length, mm	25.07 ± 1.86
Central corneal thickness, μm	543.53 ± 37.43
Preoperative average pRNFL thickness, μm	63.73 ± 13.74
Preoperative average mGC/IPL thickness, μm	60.38 ± 9.02
Preoperative MD of VF, dB	−17.93 ± 8.98
Preoperative PSD of VF, dB	8.08 ± 3.68
Follow-up period, year	0.67 ± 0.02

pRNFL, peripapillary retinal nerve fiber layer; mGC/IPL, macular ganglion cell-inner plexiform layer.

Data are mean ± standard deviation unless otherwise indicated.

TABLE 2. Changes of the Parameters of OCT-A Before and After Glaucoma Surgery

Variables	Preoperative	Postoperative 1 Week	Postoperative 1 Month	Postoperative 3 Months	P Value[*]	P Value[†]	P Value[‡]
IOP, mm Hg	25.13 ± 6.82	12.00 ± 1.08	14.97 ± 3.96	15.48 ± 1.03	**<0.001**	**<0.001**	0.166
Intradisc superficial VD, %	43.87 ± 7.18	43.94 ± 5.45	43.27 ± 7.44	44.45 ± 6.23	0.730	0.322	0.419
Intradisc deep VD, %	18.40 ± 9.40	30.37 ± 8.21	35.13 ± 8.53	34.23 ± 8.77	**<0.001**	**0.013**	0.910
Superficial VD within the peripapillary atrophy, %	10.23 ± 5.22	11.45 ± 4.74	10.15 ± 4.97	11.57 ± 6.25	0.549	0.560	0.246
Deep VD within the peripapillary atrophy, %	9.33 ± 4.88	9.49 ± 5.08	11.00 ± 7.24	9.96 ± 6.16	0.692	0.713	0.542
Macular superficial VD, %	49.60 ± 5.19	50.19 ± 5.74	50.53 ± 7.15	50.72 ± 6.96	0.745	0.626	0.835
Macular deep VD, %	52.53 ± 6.59	51.44 ± 5.23	51.67 ± 5.94	52.53 ± 6.59	0.816	0.428	0.626
Superficial FAZ area, pixel area	1292.67 ± 187.37	1260.04 ± 178.61	1245.52 ± 178.61	1235.16 ± 150.24	0.930	0.312	0.734
Deep FAZ area, pixel area	1310.67 ± 172.92	1295.35 ± 172.92	1273.33 ± 161.55	1250.42 ± 142.38	**0.018**	**0.002**	0.189
Image quality score	62.45 ± 6.28	61.33 ± 5.95	61.82 ± 6.73	63.02 ± 6.11	0.528	0.594	0.555

Data are mean ± standard deviation unless otherwise indicated. Factors with statistical significance are shown in bold.

[*] Paired *t*-test between preoperative and postoperative 1 week.

[†] Paired *t*-test between preoperative and postoperative one month.

[‡] Paired *t*-test between postoperative one month and three months.

TABLE 3. Distribution of the Patients Showing Significant Changes in the Parameters of OCT-A at Postoperative one month After Glaucoma Surgery

OCT Angiography Parameters	Progression After Glaucoma Surgery		Total	P value[*]
	Progressor	Non-Progressor		
Intradisc deep VD				
Increase	2	20	22	0.015
No Change	23	33	56	
Decrease	5	5	10	
Deep FAZ area				
Increase	4	7	11	0.027
No Change	26	39	65	
Decrease	0	12	12	

[*] χ^2 test.

poor quality or contained motion artifacts. Interobserver agreement in terms of VD measurement was excellent (ICC = 0.916; 95% CI, 0.877 – 0.953; $P < 0.001$).

The baseline patient characteristics are listed in Table 1. The mean patient age was 57.14 ± 15.76 years, and 26 (29.5%) were female patients. All patients were taking the maximum tolerated glaucoma medication, and 10 (11.4%) had a previous history of glaucoma surgery. A majority of patients had trabeculectomy (70.5%) followed by Express shunt insertion and Ahmed drainage device implantation.
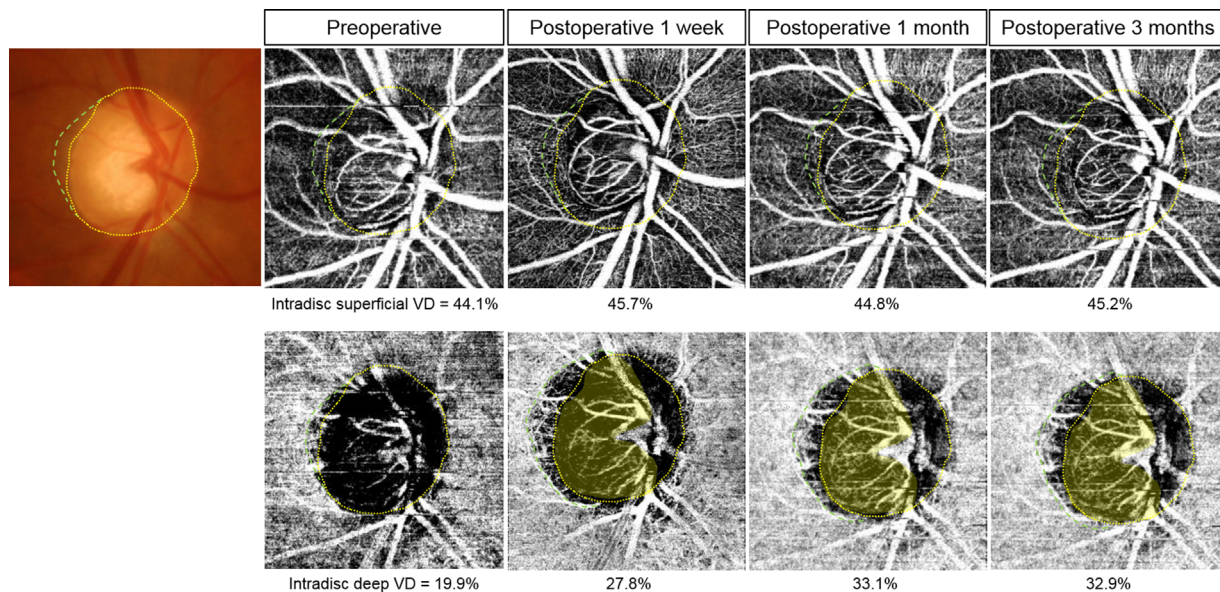

Preoperative	Postoperative 1 week	Postoperative 1 month	Postoperative 3 months

Intradisc superficial VD = 44.1%   45.7%   44.8%   45.2%

Intradisc deep VD = 19.9%   27.8%   33.1%   32.9%

FIGURE 2. Representative case showing serial changes in the VD after glaucoma surgery. Among several VD parameters measured in the present study, intradisc VD in the deep vascular layer exhibited significant changes before and after glaucoma surgery (images on the bottom row; *yellow shaded area*). This change was significant between the preoperative period and postoperative one week and one month. Intradisc VD did not differ significantly between postoperative one month and three months.

TABLE 4. Comparison Between Progressor and Non-Progressor After Glaucoma Surgery

Variables	Progressor (n = 30)	Non-Progressor (n = 58)	P Value
Age, y	51.40 ± 17.83	60.10 ± 14.14	0.084[*]
Female	4 (13.3%)	22 (37.9%)	**0.025**[†]
Previous glaucoma surgery	4 (13.3%)	6 (10.3%)	0.730[†]
Type of glaucoma surgery			0.306[†]
Trabeculectomy	21 (70.0%)	12 (70.0%)	
Express shunt	4 (13.3%)	4 (13.3%)	
Ahmed drainage device	5 (16.7%)	5 (17.7%)	
Type of medications			
β-blocker	29 (96.7%)	55 (94.8%)	0.579[†]
α-agonist	28 (93.3%)	53 (91.4%)	0.553[†]
Carbonic anhydrase inhibitors	28 (93.3%)	55 (94.8%)	0.558[†]
Prostaglandin	28 (93.3%)	55 (94.8%)	0.558[†]
Spherical equivalent, diopters	−3.21 ± 4.07	−1.45 ± 2.22	0.096[*]
Axial length, mm	25.43 ± 1.97	24.86 ± 1.82	0.361[*]
Central corneal thickness, μm	549.25 ± 40.36	540.67 ± 36.84	0.527[*]
Preoperative			
BCVA	0.53 ± 0.24	0.48 ± 0.23	0.300[*]
IOP, mm Hg	35.13 ± 6.94	28.07 ± 7.72	**0.005**[*]
Average pRNFL thickness, μm	68.36 ± 12.57	61.23 ± 14.06	0.121[*]
Average mGC/IPL thickness, μm	61.90 ± 12.36	59.75 ± 7.57	0.538[*]
MD of VF, dB	−13.71 ± 8.44	−20.20 ± 8.67	**0.028**[*]
PSD of VF, dB	7.06 ± 3.60	8.63 ± 3.71	0.205[*]
Preoperative MD slope, dB/year	−0.20 ± 0.31	−0.09 ± 0.30	0.091[*]
Intradisc deep VD, %	18.40 ± 9.57	13.72 ± 6.26	0.057[*]
Deep FAZ area, pixel area	1260.34 ± 177.34	1310.69 ± 174.21	0.194[*]
Postoperative			
BCVA	0.51 ± 0.21	0.47 ± 0.22	0.399[*]
Use of hypotensive medication	8 (26.7%)	10 (17.2%)	0.267[†]
IOP, mm Hg	14.97 ± 4.03	14.04 ± 3.78	0.454[*]
Percent IOP reduction, %	61.20 ± 19.49	57.72 ± 22.06	0.469[*]
SD of postoperative IOP, mm Hg	3.51 ± 2.50	1.95 ± 1.82	0.001[*]
Average pRNFL thickness, μm	52.43 ± 5.89	56.10 ± 5.30	0.067[*]
Average mGC/IPL thickness, μm	51.83 ± 6.13	55.43 ± 4.33	0.093[*]
MD of VF, dB	−18.68 ± 8.61	−22.67 ± 9.26	0.186[*]
PSD of VF, dB	8.98 ± 3.14	8.86 ± 3.73	0.914[*]
MD slope including preoperative VF, dB/year	−1.75 ± 0.63	−0.17 ± 0.59	**<0.001**[*]
Postoperative MD slope, dB/year	−1.51 ± 0.54	−0.14 ± 0.94	**<0.001**[*]
Intradisc deep VD, %	28.13 ± 8.53	31.21 ± 11.22	0.192[*]
Change of intradisc deep VD	−1.27% ± 2.19%	17.48% ± 5.63%	**0.008**[*]
Deep FAZ area, pixel area	1193.33 ± 161.55	1241.72 ± 162.64	0.276[*]
Change of deep FAZ area, pixel area	−117.33 ± 47.51	−118.62 ± 43.07	0.912[*]
Follow-up period, y	0.67 ± 0.02	0.66 ± 0.03	0.744[*]

SD, standard deviation; mGC/IPL, macular ganglion cell-inner plexiform layer.

Data are mean ± standard deviation unless otherwise indicated. Factors with statistical significance are shown in bold.

[*] Student's t-test.

[†] χ^2 test.

The mean spherical equivalent refractive error was −2.07 ± 3.04 D, and the mean axial length was 25.07 ± 1.86 mm. The preoperative average RNFL thickness and GC/IPL thickness were 63.73 ± 13.74 μm and 60.38 ± 9.02 μm, respectively. The preoperative MD and PSD of the VF were −17.93 ± 8.98 dB and 8.08 ± 3.68 dB, respectively. The total follow-up period was 0.67 ± 0.02 years after surgery.

The mean preoperative IOP of 25.13 ± 6.82 mm Hg was reduced significantly to 12.00 ± 1.08 mm Hg at one week ($P < 0.001$), 14.97 ± 3.96 mm Hg at one month ($P < 0.001$), and 15.48 ± 1.03 mm Hg at three months after glaucoma surgery. Preoperative and postoperative changes in the microvasculature detected by OCT-A are listed in Table 2. A significant increase in the VD was observed after surgery in the deep vascular layer of the intradisc area ($P < 0.001$). A significant decrease in the FAZ area was observed after surgery in the deep vascular layer of the macula ($P = 0.018$). These changes were significant between the preoperative period and postoperative one week and one month. Changes in VD were not significant between postoperative one month and postoperative three months. Additionally, significant changes in the intradisc deep VD and FAZ area in the deep vascular layer were found based on test−retest variability using 15 images of 15 stable glaucoma patients that were obtained within a three-month period. The 95% Bland−Altman limits of agreement between measurements were −1.47 and 1.04 for the intradisc deep VD and −1.55 and 1.11 for the FAZ area in the deep vascular layer. These values were used to classify patients with significant changes (Table 3). After glaucoma surgery, 20 eyes exhibited an increase in the intradisc deep VD in the nonprogression group, compared with only two eyes in the progression group ($P = 0.015$). Significant

TABLE 5. Factors associated with the slope of mean deviation in glaucoma patients who undergone glaucoma surgery.

	Univariate			Multivariate		
Variables	**Beta**	**95% CI**	***P* Value**	**Beta**	**95% CI**	***P* Value**
Age, per 1 y older	0.025	0.010 to 0.039	**0.001**	0.023	0.006 to 0.041	**0.008**
Female gender	−0.141	−0.659 to 0.376	0.589			
Previous glaucoma surgery	−0.108	−0.853 to 0.637	0.774			
Type of glaucoma surgery	−0.045	−0.323 to 0.233	0.749			
Use of postoperative hypotensive medication	−0.108	−0.853 to 0.637	0.774			
Axial length, per 1 mm larger	−0.166	−0.305 to −0.028	**0.019**	−0.087	−0.217 to 0.042	0.183
Central corneal thickness, per 1 µm thickner	−0.007	−0.014 to 0.001	0.069	−0.009	−0.006 to 0.007	0.980
Preoperative average pRNFL thickness, per 1 µm thicker	−0.015	−0.034 to 0.004	0.115			
Preoperative average mGC/IPL thickness, per 1 µm thicker	−0.017	−0.050 to 0.015	0.290			
Preoperative MD of VF, per 1 dB higher	0.033	0.005 to 0.062	**0.021**	0.036	0.011 to 0.060	**0.006**
Preoperative PSD of VF, per 1 dB higher	−0.020	−0.091 to 0.052	0.584			
Preoperative IOP, per 1 mm Hg higher	−0.035	−0.064 to −0.005	**0.022**	−0.022	−0.056 to 0.011	0.189
Postoperative IOP, per 1 mm Hg higher	−0.056	−0.120 to 0.007	0.081	0.048	−0.027 to 0.123	0.205
Percent IOP reduction, per % higher	0.001	−0.010 to 0.012	0.848			
SD of postoperative IOP, per 1 mm Hg higher	−0.070	−0.178 to 0.037	0.195			
Preoperative intradisc deep VD, per 1% higher	0.049	0.020 to 0.078	**0.001**	0.050	0.024 to 0.076	**<0.001**
Change of intradisc deep VD, per 1% higher	1.065	0.542 to 1.687	**<0.001**	1.073	0.437 to 1.790	**<0.001**
Preoperative deep FAZ area, per 1 pixel area higher	−0.004	−0.007 to −0.001	0.096	−0.004	−0.007 to 0.001	0.238
Change of deep FAZ area, per 1 pixel area higher	−0.001	−0.008 to 0.006	0.730			
Image quality score	0.097	−0.123 to 0.245	0.235			
Follow-up period, year	−0.017	−0.095 to 0.054	0.238			

pRNFL, peripapillary retinal nerve fiber layer; mGC/IPL, macular ganglion cell-inner plexiform layer.
Factors with *P* < 0.1 in univariate analysis were included in multivariate analysis. Factors with statistical significance are shown in bold.

TABLE 6. Factors Associated With the Preoperative and Postoperative Slope of Mean Deviation Who Undergone Glaucoma Surgery

	Preoperative MD Slope		Postoperative MD Slope	
Variables	**Beta (85% CI)**	***P* Value**	**Beta (85% CI)**	***P* Value**
Age, per 1 y older	0.005 (0.002 to 0.009)	0.007	0.022 (0.008 to 0.035)	**0.002**
Type of glaucoma surgery	0.062 (−0.013 to 0.136)	0.105	−0.069 (−0.332 to 0.193)	0.602
Axial length, per 1 mm larger	−0.032 (−0.071 to 0.007)	0.106	−0.166 (−0.294 to −0.039)	**0.011**
Preoperative MD of VF, per 1 dB higher	0.004 (−0.001 to 0.008)	0.300	0.028 (0.002 to 0.054)	**0.036**
Postoperative MD of VD, per 1dB higher	0.005 (−0.004 to 0.014)	0.311	0.020 (−0.021 to 0.062)	0.329
Preoperative IOP, per 1 mm Hg higher	−0.007 (−0.015 to 0.001)	0.101	−0.030 (−0.057 to −0.003)	**0.030**
Postoperative IOP, per 1 mm Hg higher	−0.036 (−0.151 to 0.021)	0.410	−0.044 (−0.102 to 0.014)	0.136
Percent IOP reduction, per % higher	0.003 (−0.001 to 0.007)	0.247	0.001 (−0.010 to 0.011)	0.877
SD of postoperative IOP, per 1 mm Hg higher	−0.006 (−0.021 to 0.032)	0.533	−0.069 (−0.170 to 0.033)	0.182
Preoperative intradisc deep VD, per 1% higher	0.128 (−0.019 to 0.274)	0.999	−0.011 (−0.038 to 0.017)	0.448
Postoperative intradisc deep VD, per 1% higher	−0.004 (−0.011 to 0.003)	0.311	0.009 (−0.015 to 0.034)	0.458
Change of intradisc deep VD, per 1% higher	0.001 (−0.010 to 0.013)	0.806	0.045 (0.007 to 0.083)	**0.022**

CI, confidence interval; IOP, intraocular pressure; VF, visual field; MD, mean deviation; dB, decibel; VD, vessel density.
Factors with *P* < 0.1 in univariate analysis were included in multivariate analysis.
Factors with statistical significance are shown in bold.

decrease in the deep FAZ area was observed in 12 eyes in the nonprogression group; however, none of the eyes in the progression group exhibited a decrease (*P* = 0.027). No significant differences were evident in the other VD parameters between the nonprogression and progression groups. Therefore we decided to use intradisc VD in the deep vascular layer of the ONH and the FAZ area in the deep vascular layer of the macula at one month for further analysis. As shown in the representative case in Figure 2, intradisc VD in the deep vascular layer of the ONH exhibited gradual increase until postoperative one month and minimal change thereafter.

Among 88 eyes, 30 (34.1%) showed VF progression after glaucoma surgery up to the six-month follow-up examination. The progression and nonprogression groups had mean MD slopes of −1.75 ± 0.63 and −0.17 ± 0.59 dB/y, respectively (*P* < 0.001; Table 4). When MD slopes were separately calculated as preoperative and postoperative MD slopes, progression and nonprogression groups showed significant difference in terms of postoperative MD slope (*P* < 0.001), but not with preoperative MD slope (*P* = 0.091). Male sex (*P* = 0.025), higher preoperative IOP (*P* = 0.005), and worse preoperative MD of the VF (*P* = 0.028) were significant features associated with glaucomatous eyes with VF progression after glaucoma surgery. The standard deviation of postoperative IOP during the six-month period was significantly greater in the progression group (3.51 ± 2.50 mm Hg) compared to the nonprogression group (1.95 ± 1.82 mm Hg; *P* = 0.001). The increase in the intradisc deep VD (17.48% ± 5.63%) was statistically significant in glaucomatous eyes
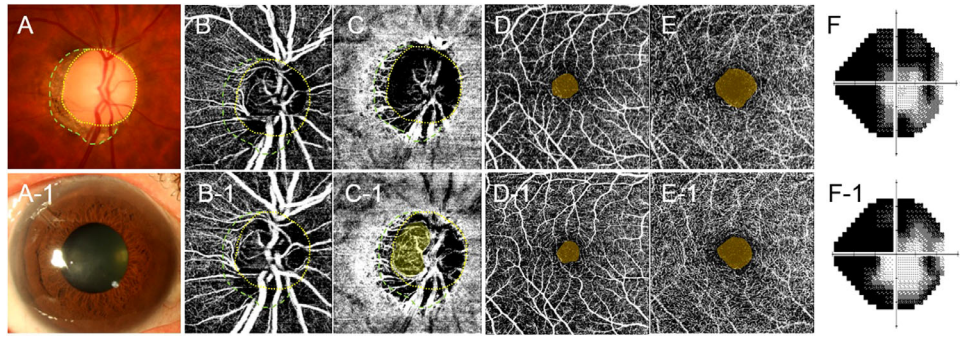
FIGURE 3. Representative case of a 61-year-old glaucoma patient with uncontrolled IOP under maximum tolerated medical treatment. **(A and A-1)** This patient underwent implantation of an Ahmed glaucoma drainage device. There was no change in the superficial vascular map before **(B)** and after surgery **(B-1)**. This patient exhibited an increase in intradisc VD on the deep vascular map at postoperative one month **(C-1**, *yellow shaded area*) compared with the preoperative image **(C)**. There was no change in FAZ area in the superficial macular layer **(D and D-1)**; however, a significant decrease in the FAZ area was observed postoperatively **(E-1**, *orange shaded area*) compared to the preoperative image **(E)** with the deep vascular map. This patient did not exhibit any VF change after glaucoma surgery **(F and F-1)**.

without progression compared to eyes with progression that exhibited a slight decrease in the intradisc deep VD (−1.27% ± 2.19%).

We performed linear regression analysis to identify the factors associated with the MD slope calculated from the whole preoperative to postoperative VFs (Table 5). A younger age ($P = 0.001$), larger axial length ($P = 0.019$), worse preoperative MD of the VF ($P = 0.021$), higher preoperative IOP ($P = 0.022$), lower preoperative intradisc VD in the deep vascular layer ($P = 0.001$), less change in the intradisc deep VD after surgery ($P < 0.001$), and a larger preoperative FAZ area ($P = 0.096$) were significant factors associated with the MD slope in the univariate analysis. Among these factors, worse preoperative MD of the VF ($P = 0.006$), lower preoperative intradisc VD in the deep vascular layer ($P < 0.001$), and less change in the intradisc deep VD after surgery ($P < 0.001$) were significantly associated with the MD slope in the multivariate analysis. When regression analysis was separately performed with preoperative and postoperative MD slopes, a younger age ($P = 0.007$) was significant factor associated with preoperative MD slope (Table 6). A younger age ($P = 0.002$), larger axial length ($P = 0.011$), worse preoperative MD of the VF ($P = 0.036$), higher preoperative IOP ($P = 0.030$), and less change in the intradisc deep VD after surgery ($P = 0.022$) were significant factors associated with the postoperative MD slope.

A representative case is shown in Figure 3. A 61-year-old male with glaucoma had uncontrolled IOP under maximum tolerated medical treatment and underwent implantation of an Ahmed glaucoma drainage device (Figs. 3A and 3A–1). There was no change in the superficial vascular map after surgery. This patient exhibited an increase in the intradisc VD in the deep vascular map at postoperative one month (Figs. 3C and 3C–1) compared with preoperative images. The FAZ area in the superficial macular layer exhibited no change; however, a significant decrease in the FAZ area was observed after surgery (Figs. 3E and 3E–1). This patient did not exhibit any VF change after glaucoma surgery (Figs. 3F and 3F–1).

By contrast, another representative case shown in Figure 4 is that of a 73-year-old male with glaucoma who underwent implantation of an Ahmed glaucoma drainage device (Figs. 4A and 4A–1) and did not exhibit any changes in VD after glaucoma surgery (Figs. 4B and 4C). This patient showed VF progression with well-controlled IOP after glaucoma surgery (Figs. 4D and 4D–1).
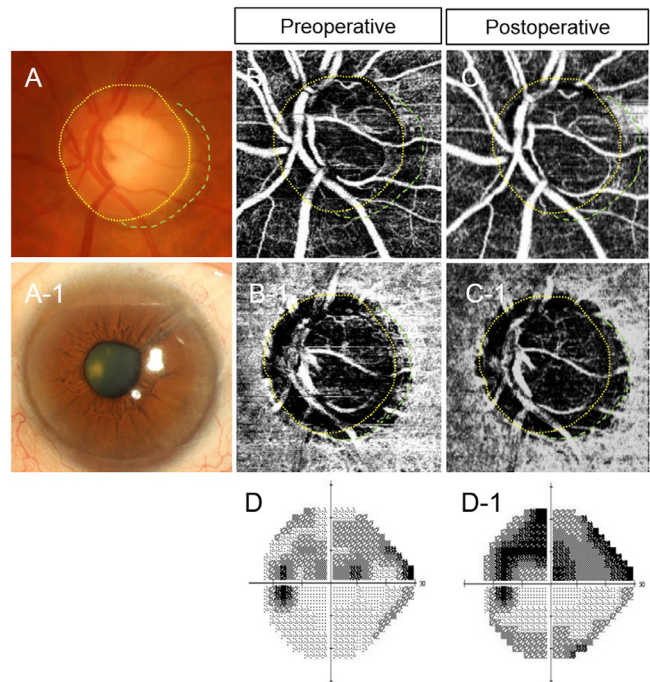

FIGURE 4. Representative case of a 73-year-old male with glaucoma who underwent implantation of an Ahmed glaucoma drainage device **(A and A-1)**. VD inside the disc area did not change after glaucoma surgery in the superficial **(B and C)** or deep vascular layer **(B-1 and C-1**; *yellow dotted area*). This patient exhibited VF progression after glaucoma surgery **(D and D-1)**.

Figure 5 shows a representative case of a 59-year-old male with glaucoma who exhibited uncontrolled IOP under maximum tolerated medical treatment in both eyes (Figs. 5B and 5C). He underwent Express implantation in both eyes with a one-month interval in between (Fig. 5A and 5D). The left eye exhibited an increase in the superficial VD on the temporal side of the disc on the superficial vascular map (Fig. 5I and 5I–1, green-shaded area) and an increase in intradisc VD on the deep vascular map (Fig. 5J and 5J–1, yellow-shaded area). This eye did not show VF progression after surgery (Fig. 5H and 5H–1). However, the right eye exhibited no change in VD (Fig. 5E and 5F) and VF progression at six months after surgery (Fig. 5G and 5G–1).
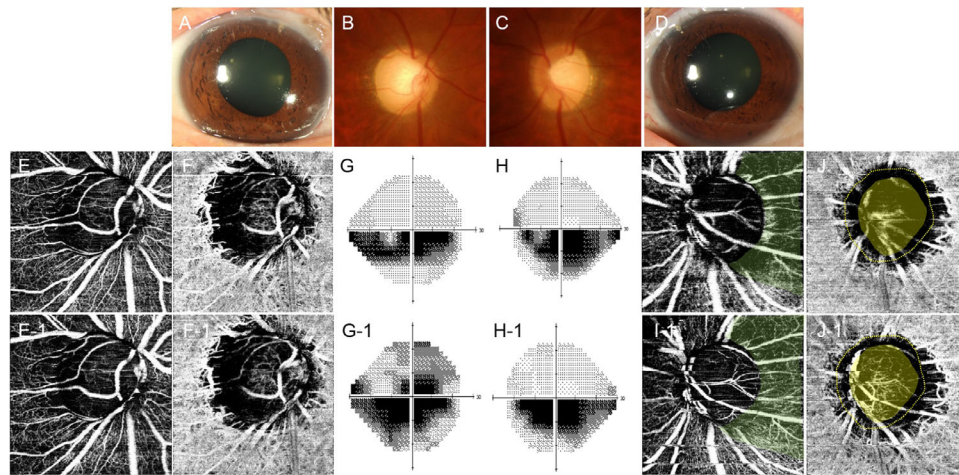
FIGURE 5. Representative case of a 59-year-old male with glaucoma who exhibited uncontrolled IOP under maximum tolerated medical treatment and underwent Express implantation in both eyes with a 1-month interval (**A, B, C,** and **D**). The right eye exhibited no change in VD in the superficial (**E** and **E-1**) or deep vascular layer (**F** and **F-1**) or VF progression at postoperative six months after glaucoma surgery (**G** and **G-1**). The left eye exhibited an increase in superficial VD in the temporal side of the disc on the superficial vascular map (**I** and **I-1**, *green-shaded area*) and an increase in intradisc VD on the deep vascular map (**J** and **J-1**; *yellow shaded area*). The left eye did not exhibit VF progression after surgery (**H** and **H-1**).

DISCUSSION

We observed VD changes in the deep vascular layer of the ONH and in the macular area up to postoperative one month after glaucoma surgery. An increase in the deep VD in the intradisc area where the LC is located was evident in 22 (25.0%) eyes and a decrease in the deep FAZ area was found in 12 (13.6%) eyes in this study. These changes, as revealed by OCT-A, differed significantly between the progression and nonprogression groups evaluated in the early postoperative period up to six months after glaucoma surgery. Preoperative intradisc VD and a change in intradisc VD in the deep vascular layer as detected by OCT-A were significant risk factors associated with postoperative VF progression in glaucoma patients who underwent glaucoma surgery due to uncontrolled IOP. These findings suggest that deep microvascular changes caused by elevated IOP could additively influence RGC damage other than that from the elevated IOP itself and contribute to glaucoma progression. Thus, with an elevated IOP, the LC tends to be compressed to the point of back bowing, resulting in axonal damage; additionally, the capillaries within the LC also become compressed. Thus IOP can affect the neurovascular complex at the level of the LC.[16]

Changes in VD after glaucoma surgery have been reported recently in several studies.[8–11] A study by Shin et al.[8] reported improvement in the superficial VD around the ONH in 19 (61.3%) of 31 eyes at postoperative three months. Factors related to the improvement in VD were maximal reduction in the IOP and change in the LC depth. A study by Zéboulon et al.[17] reported that 28.5% of the patients exhibited an improvement in VD after glaucoma surgery. Kim et al.[10] reported that VD increased at the level of the LC after glaucoma surgery in 29 (51.8%) of 56 eyes; however, no change was evident in the prelaminar area. The change in VF was related to the change in LC curvature in this study. These studies all suggest that LC compression caused by elevated IOP is likely compressing the vessels in the area; however, the exact vessels involved in this process have yet to be identified. There were changes in both superfi-

cial and deep VD in the macula or peripapillary area in these earlier studies. It is possible that the compression of laminar capillaries that originate from short posterior ciliary arteries and from vessels originating from the circle of Zinn-Haller can be resolved by IOP lowering.[18] Additionally, if the central retinal artery and branching radial peripapillary capillaries become compromised, starting from the level of the LC, this may affect the retinal microvasculature and can be observed in images of the superficial vascular layer.[19] In the present study, microvascular changes were primarily reflected in changes in intradisc deep VD, which mainly involve the vessels within the LC. Even with a mean preoperative IOP of 25.13 ± 6.82 mm Hg, prelaminar and macular superficial VD changes were minimal in our study. Therefore the IOP effect on the microvasculature seems to be mainly on the LC as opposed to a compressive effect on the retina. We also observed changes in the size of the FAZ in the deep vascular layer after lowering of the IOP. A study by Shoji et al.[11] showed that the FAZ area in the superficial vascular layer was reduced after glaucoma surgery. This suggests that superficial vessels originating from the central retinal artery may also become compressed or disturbed by elevated IOP in glaucoma patients, but they can be revived after IOP lowering. On the other hand, we only observed changes in the FAZ area in the deep vascular layer of the macula. Therefore, in this case, changes in the VD of the macula may result from shrinkage or damage of the RGC soma and reduced metabolic demand in the superficial or deep macular area. If the changes are prominent in the RGC soma and dendrites, VD changes would be only be observed in the deep vascular layer of the macula, as shown in our present study.

There were patients who exhibited no change or even patients with inverse changes in VD after IOP lowering. This may indicate a different susceptibility in the response to IOP lowering in terms of LC or VD changes. Also, this suggests indicate that an IOP reduction is not the only contributing factor for improving microvasculature after surgery. It is proposed that individual susceptibility to IOP-related stress/strain is affected by various biomechanical

factors.[20,21] Only 59% of patients exhibited LC reversal after IOP lowering.[22] The rate of VD increase after IOP lowering has been reported with wide variability, from 13.6% in the present study to 61.3% in other reports. Therefore monitoring the responses of the LC or VD to IOP lowering may be important in managing glaucoma patients and predicting their disease course. Yet, no studies have examined the role of reversal or improvement in LC or VD changes with respect to future glaucoma progression. We observed VF progression up to six months after glaucoma surgery and found that eyes with VD improvement in the LC region tended to exhibit less progression. Eyes with lower preoperative VD and a greater increase in VD in the LC region after surgery had a slower rate of VF progression. On the other hand, this could be interpreted as eyes with greater compression of the vessels at the level of the LC due to elevated IOP possibly benefitting from surgery to a greater degree because IOP lowering improves both structural and vascular compression of the LC and vessels. IOP lowering by surgery helps in terms of relieving the mechanical stress to the LC and also the ischemic insults caused by compromised vessels. Eyes that had less compressed vessels from an elevated IOP and insignificant changes from IOP lowering tended to progress faster. These progressed eyes might already have incurred prominent changes in the LC, and change in the vessels not restored by IOP lowering from glaucoma surgery or their response to IOP lowering have been minimal compared to eyes with prominent beneficial changes. A previous study showed that changes in the FAZ area were correlated significantly with the preoperative FAZ area and preoperative foveal sensitivity.[11] This also suggests that eyes with more compromised vessels and dysfunctional RGCs due to ischemic insults caused by elevated IOP would tend to exhibit a greater VD response to IOP lowering. Altogether, we suggest that VD changes after IOP lowering have an important impact on future functional deterioration in glaucoma patients. Treatment to improve blood flow may be beneficial to glaucoma patients with a tendency or vascular compromise due to elevated IOP as detected by OCT-A. Additionally, OCT-A can be used to identify glaucoma patients who are susceptible to compromised microvasculature from elevated IOP.

Our study had several limitations. Our follow-up period was six months. There was a study showing that the macular change in VD measured in the FAZ area was observed up to 12 months after glaucoma surgery.[11] We decided to use the VD values at postoperative one month, given that VD measurements did not differ between postoperative one month and three months. However, there might have been patients with a delayed VD response to IOP lowering, which would affect our results. In this present study, we want to specifically look at the short-term effect of VD changes on RGC function after lowering the IOP through glaucoma surgery. More long-term observations may be confounded by the natural course of the disease or other progression risk factors. Additionally, even there were patients with delayed VD response after postoperative one month, these patients would be classified into the progression group. Therefore this could be interpreted that patients with no response or delayed response tended to show progression after glaucoma surgery. OCT-A imaging is an emerging technique; it has limitations in the analysis of segmented layers, especially in the deeper layers because of artifacts of vascular shadowing or projection on the underlying tissues. Also, VD measurements may not completely represent anatomical vessels. The deep VD at the intradisc area was considered to reflect capillaries at the level of the LC in the present study. However, our study evaluated the change in VD in the same area of each patient, which may minimize the effects of any OCT-A visualization limitations. The VD in the prelaminar tissue exhibited minimal changes after surgery; thus, any artifacts present might not have affected the findings. Lastly, preoperative intradisc VD was lower in the non-progressor group, and the postoperative intradisc VD was similar between the non-progressor and progressor groups. This may have maximized the rate of change in VD of the non-progressor group. Also, preoperative MD was different between progressor and non-progressor groups. Patients with worse preoperative MD may have less remaining RGCs that may result in smaller change of the MD slope and these points should be considered in interpreting the findings.

In conclusion, we observed VD changes in the deep vascular layer of the ONH and the macular area up to postoperative one month after glaucoma surgery. An increase in the VD within the LC region after IOP lowering by glaucoma surgery was beneficial for VF progression in glaucoma patients with uncontrolled IOP. Applying OCT-A to evaluate the changes in microcirculation at the level of the LC may be highly useful, with respect to providing a more accurate prognosis for glaucoma patients who undergo glaucoma surgery. These findings suggest that IOP lowering is important for not only reducing the mechanical effects on the RGC axons but also enhancing blood flow to the ONH axons to preserve their function.

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