Optic Disc Vascular Density in Normal-Tension Glaucoma Eyes with or without Branch Retinal Vessel Occlusion

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Abstract

We analyzed the vascular densities (VDs) of the optic disc areas in eyes with normal-tension glaucoma (NTG) according to branch retinal vessel occlusion (BRVO) status. The VDs of the optic discs and peripapillary areas of 68 patients with NTG + BRVO (eyes with BRVO and fellow eyes with NTG alone) and 37 patients with NTG alone (controls) were measured on binarized angiographic images obtained via swept-source optical coherence tomography angiography. Disc VDs were subdivided into large vessel and small vessel VDs. VD measurements were compared among groups and correlations were assessed. The small vessel and large vessel VDs of the optic disc and peripapillary area differed significantly among eyes in the control, NTG alone, and NTG + BRVO groups (all $P < 0.001$). More optic disc VDs were significantly larger and fewer were significantly smaller in eyes with BRVO, compared to fellow eyes and control eyes. Large optic disc VD was negatively correlated with small optic disc VD ($r = -0.697$, $P < 0.001$). Peripapillary VD was lower in eyes with BRVO than in control eyes, but not in fellow eyes ($P < 0.001$ and $P = 0.975$, respectively). In conclusion, significant disc and peripapillary VD changes were observed in eyes with BRVO. However, larger optic disc VD and smaller VD were observed in fellow eyes with NTG alone, but not in control eyes, suggesting that larger optic disc VD may contribute to NTG development in patients with BRVO.

Introduction

As association between retinal vein occlusion (RVO) and glaucoma has been documented in many previous studies.[1-6] The prevalence of normal-tension glaucoma (NTG) was reported to be higher in eyes with RVO than in the general population. [1] The pathogenesis may be explained by abnormal disc anatomy, elevated intraocular pressure (IOP), and the effects of various vascular factors. In the Ocular Hypertension Treatment Study, a greater cup-to-disc ratio was associated with RVO development in patients with elevated IOP.[7] Changes in disc hemodynamics may also link RVO and glaucoma, especially in eyes with NTG; such changes play pathogenic roles in both diseases.[8-10]

Recently, optical coherence tomography angiography (OCTA) has been extensively used to analyze the vascular structures of the retina and disc area; OCTA facilitates detailed, noninvasive evaluation of retinal and choroidal microvascular structures. The results of OCTA studies have supported the notion that hemodynamic changes may trigger glaucoma. Such studies have revealed reduced vascular densities (VDs) of the optic disc and peripapillary area in eyes with glaucoma, including NTG.[11-14] Reduced VD has been associated with disease severity and progression.[15-17]

Given that pathogenic hemodynamic parameters are shared by eyes with NTG and eyes with RVO, an analysis of vessel structures around the disc in patients with these diseases might afford useful insights into the roles played by vascular changes. Here, we identified changes in the vascular structures of the optic disc and peripapillary area; we used OCTA to quantitatively analyze the VDs of eyes with NTG, according to branch retinal vein occlusion (BRVO) status.

Results

Patient demographics and clinical features

In total, 68 patients with NTG + BRVO (68 eyes with NTG + BRVO and 68 fellow eyes with NTG alone) and 37 patients with NTG alone (74 control eyes) were included in this study. The mean patient age was 66.97 years. There were no significant differences in age, sex, diabetes mellitus status, cardiovascular disease status, or cerebrovascular disease status between patients with NTG + BRVO and controls (all $P > 0.076$). Hypertension was more common in patients with NTG + BRVO than in controls ($P < 0.001$). Patient demographics are summarized in Table 1.

Mean BCVA values were lower in eyes with NTG + BRVO than in NTG fellow eyes and controls ($P = 0.004$ and $P < 0.001$, respectively). No other ocular parameter differed significantly among eyes with NTG + BRVO, NTG fellow eyes, and controls (all $P > 0.66$). Ocular parameters are summarized in Table 2.

Comparison of VCs among groups

Although the total VD of the optic disc area did not differ between patients with NTG, according to BRVO status (0.485 ± 0.033 vs. 0.484 ± 0.082; $P = 0.952$), the small vessel and large vessel VDs in the disc area significantly differed between groups (0.232 ± 0.056 vs. 0.274 ± 0.045 and 0.260 ± 0.068 vs. 0.210 ± 0.053; both $P < 0.001$). Peripapillary VD also significantly differed between groups (0.282 ± 0.046 vs. 0.296 ± 0.038; $P = 0.021$) (Figure 1).

When eyes were divided into NTG controls, eyes with NTG + BRVO, and fellow eyes with NTG alone (NTG fellow eyes), the large vessel VD was highest in eyes with NTG + BRVO, followed by the NTG fellow eyes and NTG controls; the small vessel VD exhibited the opposite order ($P < 0.001$ and $P \leq 0.046$, respectively). Eyes with NTG + BRVO exhibited lower small vessel and peripapillary VDs, and higher large vessel VDs, compared to both NTG controls and NTG fellow eyes (all $P \leq 0.036$). NTG fellow eyes exhibited a higher large vessel VD and a lower small vessel VD than did NTG controls ($P < 0.001$ and $= 0.007$, respectively) (Table 3).

Correlation analysis of VDs

Total, small vessel, and peripapillary VDs were negatively correlated with BCVA values ($r = -0.147$, -0.237, and -0.311; $P = 0.034$, 0.001, and <0.001, respectively). Large vessel VD was positively correlated with BCVA ($r = 0.159$, $P = 0.023$). Disc VDs were correlated with refractive error and axial length (all $P \leq 0.015$) (Table 4). Large vessel VD was negatively correlated with small vessel VD ($r = -0.697$, $P <0.001$) (Figure 2A). This correlation persisted when eyes were divided into groups ($r = -0.775$, -0.559, and -0.603; all $P < 0.001$) (Figure 2B, 2C, and 2D). Peripapillary small vessel VDs were positively correlated with total and small vessel VDs of the optic disc ($r = 0.307$ and 0.545; both $P < 0.001$) and negatively correlated with large vessel VD of the optic disc ($r = -0.226$; $P = 0.001$) (Figure 3).

Discussion

An understanding of hemodynamic changes in the optic disc area may yield valuable insights into the pathogenesis of NTG and BRVO. OCTA enables noninvasive visualization of vessels in the retina and optic disc, as well as quantification of vessel parameters, thus imparting detailed information regarding hemodynamic changes associated with disease. Here, we quantitatively analyzed the VDs of optic disc vessels evident on OCTA images of eyes with NTG, according to BRVO status; we compared these findings between and among groups. We found differences in the VDs of the optic disc and peripapillary area between eyes with NTG, according to BRVO status; we also found correlations between the VDs of large and small vessels in the disc and peripapillary area. Our principal findings were that BRVO was associated with enhanced large vessel VD and reduced small vessel VD in the optic disc. This was evident in both eyes with NTG + BRVO and fellow eyes with NTG alone. Furthermore, the large vessel and small vessel VDs differed significantly between fellow eyes with NTG alone and control eyes, suggesting that such changes may contribute to NTG development in patients with BRVO. Peripapillary VD was significantly reduced only in eyes with NTG + BRVO, suggesting that the change may be attributable to BRVO.

The contributions of large and small vessels to the disc VD differed between eyes with NTG, according to BRVO status. The mean VD of large vessels was higher, whereas the mean VD of small vessels was lower, in patients with NTG + BRVO. Because factors that might affect disc vasculature (e.g., age, comorbid diabetes, refractive error, and axial length; Table 4) were comparable among the groups, our interpretation may be valid. Engorgement of large vessels (especially veins) may be followed by attenuation of small vessels in eyes with BRVO. The peripapillary VDs were also lower in eyes with BRVO. The negative apparent correlation between large and small vessel VDs supports this notion. The optic disc head occupies a limited space; enhanced large vessel volume caused by congestion may trigger mechanical compression of small vessels. However, the detailed underlying mechanism requires further investigation.

The fellow eyes in patients with BRVO exhibited a greater large vessel VD and a lower small vessel VD, compared to the control eyes, suggesting that underlying systemic factors affect both eyes in patients with BRVO. Hypertension is a possible contributing factor; this demographic differed between patients with BRVO and controls. In a previous study, we showed that patients with BRVO exhibited more rapid glaucoma progression in their fellow eyes, compared to patients with glaucoma who did not develop BRVO.[18] The difference in fellow eye hemodynamics between patients with BRVO and controls, observed in the present study, might be relevant in this context.

Here, we also found that the NTG fellow eyes in patients with BRVO exhibited a significantly lower small vessel VD in the optic disc, compared with NTG control eyes. The peripapillary VD parameters did not differ between the NTG fellow eyes in patients with BRVO and NTG controls, suggesting that a small vessel VD change in the optic disc may accelerate glaucoma progression in the glaucomatous fellow eyes in patients with BRVO.[18] Systemic factors may trigger changes in the disc VDs of both eyes, thereby increasing the proportion of large vessels in patients who develop BRVO, followed by more prominent changes. Because this was a cross-sectional study, we could not determine whether the phenomenon was a cause or a result of BRVO.

Blood flows from two principal sources to the optic disc. The superficial layers of the optic nerve head (i.e., the RNFL) are supplied by the central retinal artery; the deeper layers (i.e., the prelaminar, lamina cribrosa, and retrolaminar regions) are supplied by the posterior ciliary artery.[19] Analysis of respective layers would yield detailed information regarding whether the observed changes reflect alterations in branches of the central retinal or posterior ciliary arteries. However, the resolution of current OCTA systems is inadequate for such analysis; it may be achieved in the future by using more powerful angiographic imaging systems.

The peripapillary VDs of the entire region and all four quadrants were lower in eyes with BRVO than in fellow eyes and controls, consistent with the results of a previous study by Shin et al.[20] Notably, Shin et al. reported that various peripapillary microvascular parameters were lower in fellow eyes in patients with RVO. Most vessels visible on OCTA scans of the peripapillary area are retinal, radial peripapillary capillaries.[21] These radial peripapillary capillaries branch from the central retinal artery; thus, lower peripapillary VD can be largely explained by reduction of perfusion from the central retinal artery, perhaps attributable to the venous engorgement of eyes with BRVO and the negative correlation between the large vessel VD of the optic disc and the peripapillary VD, despite the weak correlation. However, this may be less important than in the optic disc area, as the peripapillary area is not a limited space. Other possible causes of reduced central retinal artery perfusion include capillary attenuation attributable to vasospasm, atherosclerosis, or shunting.

Our study had limitations inherent to all cross-sectional retrospective analyses. As mentioned above, we could not investigate causal relationships between vessel changes and disease development; we showed only that hemodynamic changes are evident. However, to the best of our knowledge, this study was the first to quantitatively analyze disc vessel morphology in eyes with NTG, according to BRVO status. Because hemodynamic factors play important pathophysiological roles in both NTG and BRVO, we believe that the results deepen our understanding of the pathogenesis of both diseases.

In conclusion, we measured VDs of the optic disc area of eyes with NTG, according to BRVO status; we revealed enhancement of large vessel VD and reduction of small vessel VD, as well as reduction of peripapillary VD, in eyes with BRVO. The large vessel VD was significantly enhanced and the small vessel VD was significantly reduced in fellow eyes (with NTG alone) in patients with BRVO, suggesting that hemodynamic changes may contribute to NTG development in patients with BRVO. Our results suggest that the hemodynamics around the disc area differ in eyes with NTG, according to BRVO status, and may be associated with disease development or progression. Prospective follow-up studies with larger samples are required to confirm our findings.

Methods

This observational case-control study was performed using the medical records of consecutive patients with NTG (with or without BRVO) who visited Seoul St. Mary's Hospital (Seoul, Korea) between March 2018 and March 2020. The study was approved by Institutional Review Board of Seoul St. Mary's Hospital, which waived the requirement for written informed consent because of the retrospective nature of the study (KC18RESI0852). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Patients

NTG diagnostic criteria were: (1) glaucomatous optic disc change (i.e., rim thinning, disc hemorrhage, rim notch, or vertical cup-to-disc ratio greater than that of the other eye by ≥ 0.2-fold) and glaucomatous visual field (VF) loss (i.e., pattern standard deviation [P < 0.05] or glaucoma hemifield test result [P < 0.01] outside the normal limits, exhibiting a consistent pattern in the Bjerrum areas of both VFs); (2) maximum IOP < 22 mm Hg (without glaucoma medications) as determined by repeated measurements performed on different days; and (3) an open angle on gonioscopic examination.

BRVO was defined as retinal venous obstruction in a localized area of the retina, characterized by scattered superficial and deep retinal hemorrhages, venous dilation, intraretinal microvascular abnormalities, and occluded and sheathed retinal venules. BRVO was diagnosed at the time of initial NTG diagnosis or during NTG follow-up.

The exclusion criteria were: (1) spherical refraction > ±6.0 diopters; (2) glaucoma with BRVO in both eyes; (3) history of any retinal disease other than BRVO; (4) history of eye trauma or surgery, with the exception of uncomplicated cataract surgery; and (5) any optic nerve disease other than glaucoma.

All patients underwent a complete ophthalmic examination, including assessment of best-corrected visual acuity (BCVA) and refractive error; slit-lamp biomicroscopy; gonioscopy; IOP measurement using Goldmann applanation tonometry; axial length assessment via ocular biometry (IOLMaster; Carl Zeiss Meditec, Dublin, CA, USA); stereoscopic photography and red-free fundus photography (Canon, Tokyo, Japan); Humphrey VF testing using the Swedish Interactive Thresholding Algorithm Standard 24-2 test (Carl Zeiss Meditec); optical coherence tomography (Carl Zeiss Meditec) of the retinal nerve fiber layer (RNFL); and OCTA of the disc area (DRI OCT Triton, Topcon Corporation, Tokyo, Japan). OCTA data regarding eyes with BRVO were obtained during the inactive phase of BRVO (i.e., in the absence of edema and active hemorrhage). BCVA was converted into the logarithm of the minimal angle of resolution to allow statistical analysis.

Image analysis

En face OCTA images (3 x 3 mm^2 in area, centered at the optic disc) were obtained for each eye. For eyes with macular edema and hemorrhage, OCTA were taken after subsidence of fluid and hemorrhage. For VD analysis, a combined image was automatically generated by ImageNet software (ImageNet 6, ver. 1.19.11030, Topcon Corporation); the superficial and choriocapillaris layers were fused (Figure 4A). VD was quantified as follows using FIJI software (an expanded version of ImageJ ver. 1.51a, available at fiji.sc). First, all vessels were traced using the Frangi vesselness plugin (Figure 4B). Large vessel areas were traced using the Tubness plugin (Figure 4C). Then, the total, small, and large vessel VDs were measured in regions of interest of the optic disc and peripapillary area; the final figures were calculated by dividing the vessel area by the total region of interest (Figure 4D and 4E). Peripapillary VDs were subdivided into those of four quadrants: superotemporal (ST), superonasal (SN), inferonasal (IN), and inferotemporal (IT) (Figure 4E). The means of two measurements of each VD were used. Only clear images with quality scores > 30 that did not exhibit blurring attributable to motion were analyzed.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (version 23.0.1; IBM Corp., Armonk, NY, USA). Independent t-tests and one-way analysis of variance were used to compare continuous variables among and between groups after confirmation of a normal distribution. The Mann-Whitney U test and Kruskal-Wallis test were employed when a normal distribution could not be confirmed. Fisher's least significant difference test served as the post hoc test after one-way analysis of variance. Categorical variables were compared between groups using the chi-squared test. Standardized adjustment was used as the post hoc test after the chi-squared test. A P-value < 0.05 was considered statistically significant.

Declarations

Competing interests: The authors declare no competing interests.

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Author Contributions Statement

Contributions were as follows: J.B.: conception and design of the study, writing manuscript text, preparing figures, collection and assembly of data, and data analysis and interpretation; S.J.J. and J.H.K.: collection of data; C.K.P: conception and design of the study and supervision; H.L.P.: conception and design of the study, writing manuscript text, preparing figures, collection and assembly of data, data analysis and interpretation, and supervision; All authors reviewed the manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Tables

Table 1. Demographic and clinical parameters of patients with BRVO and controls.

Variable	NTG controls (n=37)	NTG + BRVO (n=68)	P-value
Age (years), mean±SD	66.14±10.89	67.81±10.63	0.285
Sex (male/female), n	16/21	22/46	0.118
Diabetes mellitus, n (%)	5 (14)	15 (22)	0.133
Hypertension, n (%)	4 (11)	31 (46)	<0.001*
CVD (0: no/1: yes)	4 (11)	3 (4)	0.076
BRVO: branch retinal vein occlusion; SD: standard deviation; CVD: cardio- or cerebrovascular disease.			
* P-value is significant.			

Table 2. Ocular parameters of the groups.

	NTG controls (n=74)	NTG + BRVO eyes (n=68)	NTG fellow eyes (n=68)	P-value[a]	P-value[b]	P-value[c]	P-value[d]
BCVA (logarithm of the minimal angle of resolution), mean±SD	0.08±0.11	0.21±0.26	0.11±0.18	<0.001*	<0.001*	0.326	0.004*
Refractive error (diopter), mean±SD	-0.3±2.66	-1.03±2.34	-0.95±2.45	0.156	0.083	0.117	0.867
Axial length (mm), mean±SD	24.3±1.28	24.02±1.43	23.84±1.27	0.121	0.211	0.052	0.441
IOP (mmHg), mean±SD	14.34±3.04	14.76±3.4	14.84±3.59	0.627	0.448	0.374	0.898
RNFL thickness (μm), mean±SD	83.01±17.27	80.07±21.51	83.09±20.38	0.593	0.376	0.982	0.374
VF mean deviation (dB), mean±SD	-4.07±5.79	-6.73±7.56	-5.07±6.92	0.066	0.021	0.383	0.155
Disc hemorrhage, n (%)	7 (9)	2 (3)	5 (7)	0.290	0.122	0.616	0.304

BRVO: branch retinal vein occlusion; SD: standard deviation; IOP: intraocular pressure; RNFL: retinal nerve fiber layer; VF: visual field.

a. One-way analysis of variance
b. t-test comparing control eyes and eyes with BRVO.
c. t-test comparing control and fellow eyes.
d. t-test comparing eyes with BRVO and fellow eyes.

* P-value is significant.

Table 3. Vessel densities of the groups.

Vascular density	NTG controls (n=74)	NTG + BRVO eyes (n=68)	NTG fellow eyes (n=68)	P-value[a]	P-value[b]	P-value[c]	P-value[d]
Disc total VD	0.485±0.033	0.469±0.101	0.499±0.051	0.037*	0.175	0.199	0.010*
Disc small vessel VD	0.274±0.045	0.212±0.051	0.252±0.054	<0.001*	<0.001*	0.007*	<0.001*
Disc large vessel VD	0.210±0.053	0.272±0.075	0.248±0.059	<0.001*	<0.001*	<0.001*	0.031*
Peripapillary VD	0.296±0.038	0.269±0.045	0.296±0.042	<0.001*	<0.001*	0.957	<0.001*
Peripapillary VD ST	0.318±0.057	0.277±0.056	0.308±0.051	<0.001*	<0.001*	0.263	0.001*
Peripapillary VD SN	0.273±0.053	0.255±0.055	0.286±0.048	0.003*	0.040*	0.133	0.001*
Peripapillary VD IN	0.288±0.034	0.261±0.053	0.278±0.05	0.003*	0.001*	0.225	0.036*
Peripapillary VD IT	0.316±0.041	0.282±0.054	0.308±0.058	<0.001*	<0.001*	0.361	0.004*

BRVO: branch retinal vessel occlusion; VD: vascular density; ST: superotemporal; SN: superonasal; IN: inferonasal; IT: inferotemporal.

a. One-way analysis of variance
b. t-test comparing control and eyes with BRVO.
c. t-test comparing control and fellow eyes.
d. t-test comparing eyes with BRVO and fellow eyes.

* P-value is significant.

Table 4. Correlations between VDs and clinical parameters.

Vascular density		Age	Sex	DM	HBP	CVD	BCVA	Refractive error	Axial length	IOP	RNFL thickness	VF mean deviation	Disc hemo
Disc total VD	Coefficient	-0.076	-0.076	-0.038	0.090	0.043	-0.147*	0.176*	-0.211*	-0.088	0.105	0.183*	0.016
	P-value	0.274	0.274	0.582	0.196	0.533	0.034	0.011	0.002	0.207	0.132	0.008	0.821
Disc small vessel VD	Coefficient	-0.305*	-0.058	-0.204*	-0.111	-0.019	-0.237*	-0.218*	0.169*	-0.047	-0.005	0.109	0.069
	P-value	0.000	0.409	0.003	0.111	0.790	0.001	0.002	0.015	0.505	0.940	0.118	0.326
Disc large vessel VD	Coefficient	0.163*	0.023	0.096	0.135	0.041	.159*	0.236*	-0.242*	0.031	0.025	-0.028	-0.060
	P-value	0.019	0.738	0.171	0.054	0.558	0.023	0.001	0.000	0.654	0.716	0.695	0.393
Peripapillary VD	Coefficient	-0.206*	0.125	-0.112	-0.018	0.022	-0.311*	0.034	-0.065	-0.039	0.247*	0.277*	0.027
	P-value	0.003	0.073	0.110	0.799	0.757	0.000	0.630	0.356	0.581	0.000	0.000	0.697
Peripapillary VD ST	Coefficient	-0.198*	0.102	-0.161*	-0.070	-0.042	-0.270*	-0.015	-0.030	-0.044	0.114	0.234*	0.116
	P-value	0.004	0.146	0.021	0.320	0.552	0.000	0.832	0.668	0.531	0.104	0.001	0.096
Peripapillary VD SN	Coefficient	-0.166*	0.038	-0.010	0.134	0.001	-0.319*	0.032	-0.037	-0.007	0.254*	0.162*	0.057
	P-value	0.017	0.585	0.884	0.055	0.989	0.000	0.646	0.596	0.922	0.000	0.020	0.414
Peripapillary VD IN	Coefficient	-0.146*	0.081	-0.087	-0.053	0.069	-0.244*	0.054	-0.049	-0.029	0.176*	0.233*	-0.016
	P-value	0.037	0.247	0.212	0.453	0.326	0.000	0.437	0.486	0.682	0.011	0.001	0.825
Peripapillary VD IT	Coefficient	-0.145*	0.139*	-0.128	-0.128	0.043	-0.204*	0.086	-0.092	-0.047	0.208*	0.256*	-0.076
	P-value	0.038	0.047	0.066	0.068	0.540	0.003	0.221	0.189	0.505	0.003	0.000	0.275

DM: diabetes mellitus; HTN: hypertension; CVD: cardio- or cerebrovascular disease; BCVA: best-corrected visual acuity; IOP: intraocular pressure; RNFL: retinal fiber layer; VF: visual field; VD: vascular density; ST: superotemporal; SN: superonasal; IN: inferonasal; IT: inferotemporal.

* P < 0.01 (two-tailed).

Figures

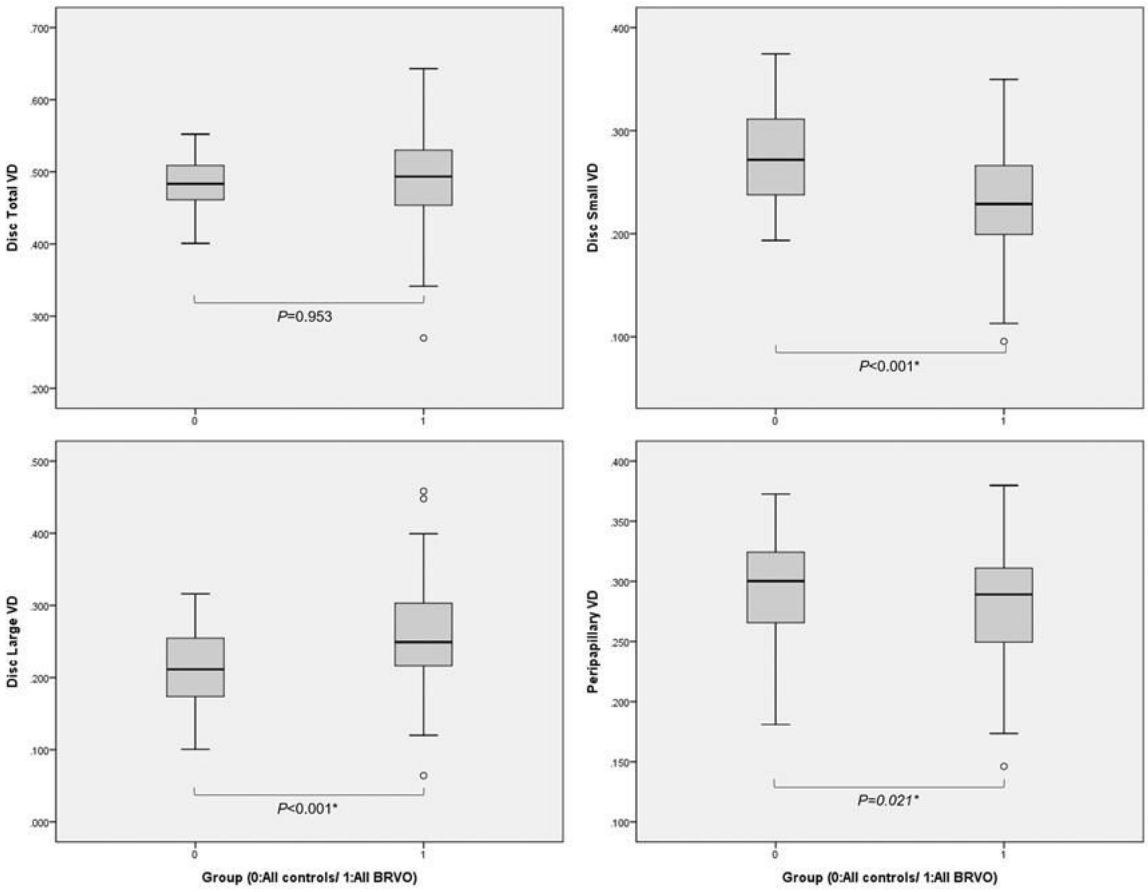

Figure 1

VDs of the disc and peripapillary areas of patients with NTG, according to BRVO status. Small and large vessel VDs in the disc area differed significantly between patients with NTG, according to BRVO status (both P < 0.001). Peripapillary VD was lower in patients with NTG +BRVO than in patients with NTG alone (P = 0.021).

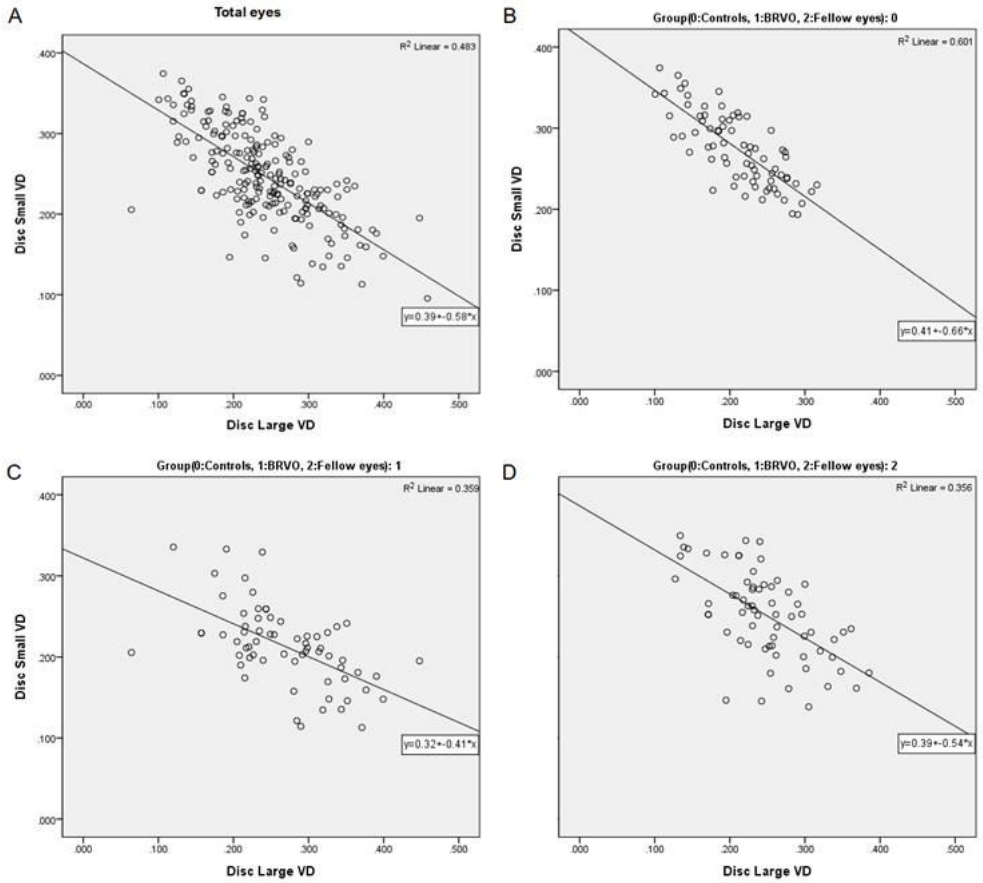

Figure 2

Correlations between large and small vessel VDs in the optic disc area. (A) Large vessel VD correlated negatively with small vessel VD. (B, C, and D). This correlation remained consistent when patients were divided into groups.

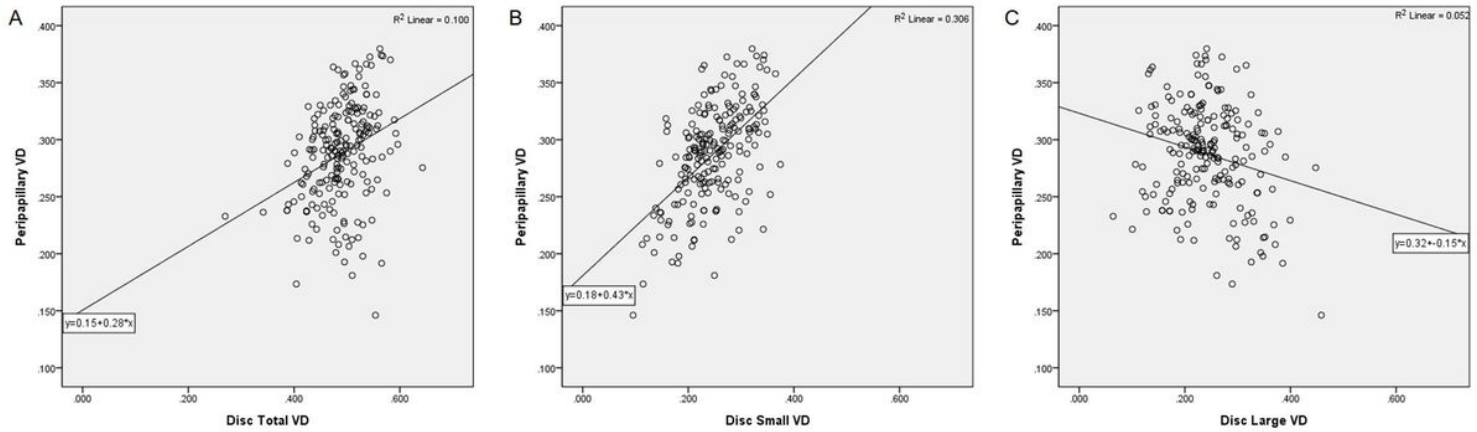

Figure 3

Correlation between disc and peripapillary VDs. (A and B) Total and small vessel VDs of the optic disc area were correlated positively with peripapillary VD. (C) Larger vessel VD of the optic disc area was correlated negatively with peripapillary VD.

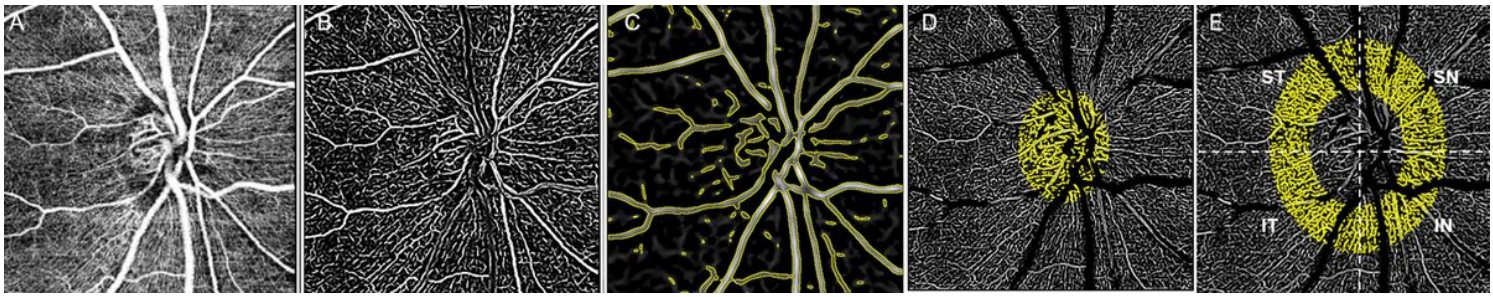

Figure 4

Measurement of vascular density. (A) En face, optical coherence tomography angiography image of 3 x 3-mm2 disc area showing vessels from two combined layers. (B) Vessels were traced using Frangi vesselness plug-in. (C) Large vessel areas were selected using Tubness plug-in. Regions of interest were selected in the optic disc (D) and peripapillary area (E). Vascular density was calculated by dividing vessel area by region of interest.