The Relationship Between Peripapillary Vascular Density and Visual Field Sensitivity in Primary Open-Angle and Angle-Closure Glaucoma

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Submitted: August 1, 2018
Accepted: November 2, 2018

Citation: Jo YH, Sung KR, Yun S-C. The relationship between peripapillary vascular density and visual field sensitivity in primary open-angle and angle-closure glaucoma. *Invest Ophthalmol Vis Sci*. 2018;59:5862–5867. https://doi.org/10.1167/iovs.18-25423

Purpose. To investigate whether the relationship between circumpapillary vascular density (cpVD) and visual field (VF) mean sensitivity (MS) differs between primary open-angle (POAG) and angle-closure glaucoma (PACG).

Methods. The cpVD and retinal nerve fiber layer thickness (RNFLT) were obtained using optical coherence tomography angiography (OCTA, AngioVue/RTVue-XR) in 146 eyes from 146 subjects (age- and VF mean deviation-matched 86 POAG and 60 PACG). Global and regional relationships (superotemporal [ST], superonasal [SN], nasoupper [NU], nasolower [NL], inferonasal [IN], inferotemoporal [IT], temporolower [TL], and temporoupper [TU] sectors) were estimated between cpVD and VF MS using multiple linear regression models controlling for the confounding variables in two disease categories. Uni- and multivariate linear regression models were built using cpVD as the dependent variable and covariates (age, intraocular pressure [IOP], axial length, signal strength index, and RNFLT) as independent variables.

Results. In PACG eyes, the cpVD was associated with the corresponding VF MS in five sectors (semipartial correlation coefficient [sr]: 0.144–0.567, $P < 0.05$): IN, IT, ST, TL, and SN, while the RNFLT showed association in four sectors (sr: 0.047–0.544, $P < 0.05$). In POAG eyes, the cpVD of all sectors was associated with the corresponding VF MS (sr: 0.246–0.574, $P < 0.05$). Greater IOP and lower RNFLT were independently associated with reduction of cpVD in the PACG group ($P = 0.002$, $P < 0.001$). In the meantime, only lower RNFLT was associated with reduction of cpVD in the POAG group ($P < 0.001$).

Conclusions. POAG and PACG eyes differed in vascular–function relationship determined by OCTA and VF MS.

Keywords: primary angle closure glaucoma, primary open angle glaucoma, optical coherence tomography angiography, visual field

Primary angle-closure glaucoma (PACG) is a leading cause of irreversible blindness globally. It caused bilateral blindness in 3.9 million people with PACG in 2010, and this number is expected to rise to 5.3 million people by 2020.[1] Although the prevalence of POAG is higher than that of PACG in most populations, PACG carries a 3-fold higher risk of developing severe and bilateral visual loss.[2]

Although intraocular pressure (IOP) is a known major risk factor for the development and progression of glaucoma, among vascular factors, optic nerve head (ONH) perfusion impairment has also emerged as an important risk factor. With the recent advent of optical coherence tomography angiography (OCTA), which allows reproducible and quantitative assessment of the parapapillary and macular microvascular status, understanding of the reduced ONH and parapapillary vessel density in glaucoma has improved considerably.[3–6]

Previous studies of the patterns of glaucomatous damage and vascular– and structure–function relationships in glaucoma are predominantly based on POAG.[7,8] In POAG, reduction of the parapapillary and macular microvasculature has been observed,[4,9,10] and the global and regional circumpapillary vascular density (cpVD) was highly correlated with corresponding visual field mean sensitivity (VFMS), especially in the moderate to severe stage of POAG.[11] Although somewhat debated, reduction of vascularity was considered to be a consequence of glaucomatous damage in the retinal nerve fiber layer (RNFL). Thus, it was proposed that reduced RNFL resulted in the subsequent decrease of parapapillary and macular vascular density (VD).[12]

However, PACG is a disease entity that differs from POAG in terms of the clinical course and pathogenic mechanisms.[13] Higher IOP elevation is observed in PACG, and causes ischemic injury to various intraocular structures, for instance, the lens, corneal endothelium, and iris. Likewise, ocular perfusion can also be altered during the process of IOP elevation, which may directly cause deterioration in the peripapillary and macular microvascular perfusion. Previous studies have reported that PACG eyes revealed significantly reduced VD than their fellow primary angle-closure suspect (PACS) eyes, which suggested that acute IOP elevation had a detrimental effect on VD.[14] Interestingly, Wang et al.[15] reported that the RNFL and macular ganglion cell thicknesses did not differ between acute primary

angle-closure (APAC) and fellow PACS eyes, although visual field (VF) sensitivity was substantially worse in APAC eyes. This implies that deterioration of VD may not be the only consequence of the reduction of the RNFL thickness in PACG eyes.[15]

Therefore, we hypothesized that PACG eyes and POAG eyes would differ in terms of the relationship among vascular, structural, and functional glaucomatous damage. Hence, we here investigated whether the relationship between cpVD and VFMS differed between POAG and PACG eyes. Glaucomatous damage usually begins as a localized RNFL defect or neuroretinal rim thinning in the early stage, which enlarges in different directions as the disease progresses. However, in the presence of elevated IOP, this regional predilection may not be a generalized feature. Thus, we compared the regional as well as the global relationships in our current analysis.

Methods

Study Participants

In this retrospective cross-sectional study, the participants who met the inclusion criteria given below were consecutively enrolled; 86 POAG and 60 age- and VF mean deviation (MD)-matched PACG eyes of persons who attended the Glaucoma Clinic at the Asan Medical Center from January 1, 2017, to August 31, 2018 were included in the final analysis. The institutional review board of Asan Medical Center approved the study protocols and methods, which adhered to the tenets of the Declaration of Helsinki.

All subjects underwent thorough ophthalmologic examinations, including measurements of best-corrected visual acuity (BCVA), IOP (with a Goldmann applanation tonometer), axial length (AL) (with IOL Master; Carl Zeiss Meditec, Dublin, CA, USA), and central corneal thickness (CCT; with ultrasound pachymetry; DGH-550; DGH Technology, Inc., Exton, PA, USA), as well as a dilated fundus examination, stereophotography of the optic disc, RNFL photography, and gonioscopy. OCTA (Angiovue; Optovue, Inc., Fremont, CA, USA) and a Humphrey field analyzer Swedish Interactive Threshold Algorithm (SITA) 24-2 VF test (Carl Zeiss Meditec) were also completed.

Both POAG and PACG groups had typical glaucomatous ONH damage, such as neuroretinal rim thinning with a vertical cup-to-disc ratio of >0.7 or asymmetry of >0.2, notching, or RNFL defects; and a compatible glaucomatous VF defect, following Anderson and Patella's criteria.[16] Patients with POAG had open angles in gonioscopic examination. PACG was diagnosed when an eye had a primary angle closure (pigmented posterior trabecular meshwork was not visible on nonindentation gonioscopy for at least 180° in the primary position and exhibited features indicative of trabecular obstruction by the peripheral iris—i.e., elevated IOP, peripheral anterior synechiae, iris whorling [distortion of the radially oriented iris fibers], "glaukomflecken" lens opacity, or excessive pigment deposition on the trabecular surface) along with glaucomatous ONH and VF defects.[17]

Inclusion criteria for all subjects were age > 18 years, BCVA ≥ 20/40, ≥ two reliable VF tests, and good-quality OCTA images (signal strength index [SSI] > 40). If both eyes met the inclusion criteria, one eye was randomly selected. Exclusion criteria were as follows: presenting IOP ≥ 30 mm Hg, uveitis, pseudo-exfoliation, ocular trauma or history of (1) any ophthalmic or neurologic disease known to affect OHN or VFMS, (2) intraocular surgery (except for uncomplicated cataract), (3) an acute primary angle-closure episode; ocular or periocular pain, nausea or vomiting, intermittent blurred vision with haloes, or experience of at least three of the following—conjunctival injections, corneal epithelial edema, mid-dilated unreactive pupil, or shallow anterior chamber.[18] Poor-quality OCTA images (SSI < 40), and unreliable VF results (fixation loss > 20%, false-positive error > 15%, and false-negative rate > 15%) were also reasons for exclusion.

Optical Coherence Tomography Angiography

All subjects underwent OCTA imaging with an AngioVue (Optovue, Inc.). The AngioVue noninvasively scans the optic disc using an 840-nm diode laser source, and provides information on the vascular structures of the retina at the capillary level. It uses the split spectrum amplitude-decorrelation angiography (SSADA) algorithm, which compares consecutive B-scans at the same location to detect dynamic flow of red blood cells.[19] The software provides VD automatically at various user-defined layers, qualitatively and quantitatively.

In this study, the peripapillary images were acquired with a 4.5 × 4.5-m scanning area centered on the optic disc. The cpVD was measured at a 1.00-mm-wide elliptical annulus extending outward from the optic disc boundary in the radial peripapillary capillary (RPC) zone (Fig. 1A). The RPC layer extends from the internal limiting membrane to the nerve fiber layer. The peripapillary region was divided into eight sectors based on the Garway-Heath map: superotemporal (ST), superonasal (SN), nasoupper (NU), nasolower (NL), inferonasal (IN), inferotemoporal (IT), temporolower (TL), and temporoupper (TU) sectors (Fig. 1A).[20]

Retinal Nerve Fiber Layer Thickness Measurement

Circumpapillary (cp)RNFL thickness (RNFLT) was also measured using the AngioVue (Optovue, Inc.). The RNFLT was assessed at a 3.45-mm-diameter circle around the optic disc in the ONH mode. The average RNFLT for eight sectors automatically appears in a ring at the outer edge of the map, which closely matched the sectors of the OCTA parameters (Fig. 1B).

Visual Field Mean Sensitivity Measurement

Standard automated perimetry (SAP) tests were completed using a Humphrey Field Analyzer (Carl Zeiss Meditec), with the SITA standard 24-2 threshold test. The VFMS at each test point was converted to the linear scale of 1/Lambert (1/L) and then averaged to obtain mean sensitivity values in each sector, according to the Garway-Heath map (Fig. 1C). Details of the VFMS calculation have been described in previous report.[21]

Statistical Analysis

Comparison between the POAG and PACG groups was performed using independent *t*-test for continuous variables and the χ^2 test for categorical variables. Multivariate linear regression analysis, adjusted for confounding factors such as age, sex, AL, IOP, and SSI, was performed to assess the relationship between sectoral cpVD, RNFLT, and corresponding VFMS. The semipartial correlation coefficient (sr) indicates that the amount of variance in the objective variable can be attributed to an explanatory variable, independent of the other covariates. The sr^2 value indicates that the proportion of total variance in the objective variable is uniquely accounted for by an explanatory variable after controlling for other covariates. A partial residual plot was used to visualize the relationship between a given explanatory variable and the objective variable after controlling for the effect of other covariates in the multivariate linear regression model. Univariate linear regression models were built using cpVD as the dependent variable and covariates (age, IOP,

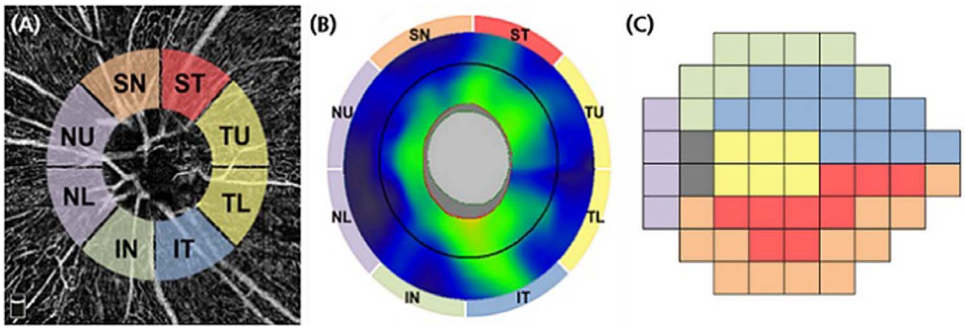

Figure 1. The circumpapillary sectors where vascular densities were measured. (**A**) Circumpapillary vascular density of the radial peripapillary capillary layer with the Garway-Heath map sectors (radius = 1.00 mm from the optic disc boundary): superotemporal (ST), superonasal (SN), nasoupper (NU), nasolower (NL), inferonasal (IN), inferotemoporal (IT), temporolower (TL), and temporoupper (TU) sectors. (**B**) Retinal nerve fiber layer thickness in the Garway-Heath map sector, and (**C**) visual field pattern map of the corresponding Garway-Heath regions.

AL, SSI, and RNFLT) as independent variables. Variables with a P value less than 0.05 in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed with SPSS software version 19.0 for Windows (SPSS, Inc., Chicago, IL, USA). For all analyses, $P < 0.05$ was considered statistically significant.

Results

There were a total of 103 eyes of 103 POAG patients and 69 eyes of 69 PACG patients that met our initial inclusion criteria. Among them, 17 eyes (16.5%) of 103 POAG eyes and 9 eyes (13.0%) of 69 PACG eyes were excluded due to unreliable VF testing and poor OCTA image quality. Eighty-six POAG and 60 age- and VFMD-matched PACG eyes were included in the final analysis. The demographic and clinical characteristics of the patients are summarized in Table 1. There were statistically significant differences between groups in terms of AL and pattern standard deviation (PSD) (respectively, $P < 0.001$), while there were no significant differences in age, sex, laterality, initial IOP, mean IOP, presence of hypertension and diabetes mellitus, CCT, SSI, VF index, VF MD, cpVD, and RNFLT between the two groups (all $P > 0.05$).

Table 1. Demographics, Visual Field, cpVD, and RNFLT Characteristics of the Participants

Characteristics	POAG, $n = 86$	PACG, $n = 60$	P Value
Age, y	64.30 ± 10.70	67.53 ± 8.81	0.056
Sex, M:F (%)†	34:52 (39.5)	20:40 (33.3)	0.445
Laterality, Rt:Lt (%)†	50:36 (58.1)	31:29 (51.7)	0.439
Initial IOP, mm Hg	15.48 ± 3.63	16.87 ± 5.45	0.088
Mean IOP, mm Hg	13.98 ± 2.18	14.37 ± 2.63	0.344
Hypertension (%)†	15 (17.4)	7 (11.7)	0.337
Diabetes mellitus (%)†	19 (22.1)	18 (30.0)	0.280
CCT, μm	532.55 ± 52.83	534.04 ± 36.76	0.860
Axial length, mm	23.96 ± 1.17	22.94 ± 0.73	<0.001*
SSI	59.26 ± 10.97	59.28 ± 10.02	0.987
Visual field			
VFI, %	80.57 ± 13.28	80.53 ± 16.68	0.988
MD, dB	−6.74 ± 4.46	−7.64 ± 5.86	0.320
PSD, dB	9.09 ± 3.90	6.29 ± 4.26	<0.001*
cpVD (%)	42.91 ± 5.58	41.86 ± 7.82	0.370
RNFLT, μm	78.44 ± 10.97	81.81 ± 13.21	0.117

VFI, visual field index; dB, decibel. Data are mean ± standard deviation or n (%) values.

* Statistically significant differences indicated for $P < 0.05$. Unless otherwise indicated, independent t-tests were used.

† χ^2 test was applied.

The global semipartial correlations between cpVD, RNFLT, and VFMS, after controlling for age, sex, IOP, AL, and SSI, are all statistically significant (sr: 0.331–0.743, all $P < 0.05$) in both groups. The sectoral semipartial correlations between cpVD, RNFLT, and VFMS according to Garway-Heath map are listed in Table 2 and Figure 2. In PACG eyes, VFMS showed a significant association with the corresponding RNFLT in the four sectors (ST, SN, IT, and IN), while cpVD showed significant association with the corresponding VFMS in five sectors (ST, SN, IT, IN, and TL). In POAG eyes, the cpVD of all sectors were significantly associated with the corresponding VF MS (sr: 0.246–0.574, $P < 0.05$) and RNFLT (sr: 0.188–0.453, $P < 0.05$).

The results of univariate and multivariate linear regression analysis using cpVD as the dependent variable and covariates (age, IOP, AL, SSI, and RNFLT) as independent variables are summarized in Table 3. In multivariate linear regression analysis with cpVD as the dependent variable, while controlling for the confounding effects of sex and SSI, greater IOP and lower RNFLT were independently associated with reduction of cpVD (respectively, B = –0.326 and 0.473, $P = 0.002$ and $P < 0.001$) in PACG group. In the meantime, only lower RNFLT was associated with reduction of cpVD (B = 0.345, $P < 0.001$) in the POAG group.

Discussion

Recent OCTA studies have revealed structural or vasculature loss in POAG and PACG eyes, as compared with normal or glaucoma suspect eyes,[4,14,22] but the patterns of regional change in POAG and PACG eyes had not been described to date. As the pathogenesis of POAG and PACG differs, it is plausible that the patterns of damage in each disease would also be different. Yarmohammadi et al.[4] reported that decreased cpVD was significantly associated with the severity of global VF damage, and the cpVD–VFMS association was stronger than the RNFL–VFMS association in POAG. Shin et al.[11] also reported a strong global and regional relationship between cpVD and VFMS in moderate-to-severe glaucoma. However, these vascular–functional relationships were not thoroughly investigated in PACG eyes.

In the present study, the vascular–function relationship as well as the structure–function relationship was evaluated, after adjusting for the confounding factors, such as age, sex, SSI, and AL, using individual VF locations matched to the corresponding cpVD sectors. In PACG eyes, VFMS showed a significant association with the corresponding RNFLT in four sectors while cpVD showed association with the corresponding VFMS

Table 2. The Semipartial Correlation Between cpVD, RNFLT, and VFMS for Each Sector, After Controlling for Confounding Factors

	RNFL-cpVD			RNFL-VFMS			cpVD-VFMS		
Groups	**sr**	**sr^2**	***P***	**sr**	**sr^2**	***P***	**sr**	**sr^2**	***P***
PACG									
Global	0.659	0.434	<0.001*	0.338	0.114	0.012*	0.418	0.175	<0.001*
ST	0.697	0.486	<0.001*	0.544	0.296	<0.001*	0.514	0.264	<0.001*
SN	0.571	0.326	<0.001*	0.336	0.113	0.011*	0.384	0.147	0.002*
IT	0.738	0.545	<0.001*	0.495	0.245	0.001*	0.567	0.321	<0.001*
IN	0.761	0.579	<0.001*	0.451	0.203	0.001*	0.445	0.198	0.001*
NU	0.471	0.222	<0.001*	0.074	0.005	0.575	0.162	0.026	0.175
NL	0.492	0.242	<0.001*	0.047	0.002	0.713	0.144	0.021	0.208
TU	0.63	0.397	<0.001*	0.206	0.042	0.106	0.196	0.038	0.101
TL	0.341	0.116	0.017*	0.177	0.031	0.242	0.437	0.191	0.001*
POAG									
Global	0.567	0.322	<0.001*	0.427	0.182	<0.001*	0.444	0.197	0.001*
ST	0.546	0.298	<0.001*	0.543	0.295	<0.001*	0.574	0.329	<0.001*
SN	0.518	0.268	<0.001*	0.339	0.115	0.009*	0.469	0.220	<0.001*
IT	0.738	0.545	<0.001*	0.507	0.257	<0.001*	0.508	0.258	<0.001*
IN	0.539	0.291	<0.001*	0.360	0.129	0.002*	0.383	0.147	0.001*
NU	0.359	0.129	0.002*	0.247	0.061	0.050*	0.252	0.064	0.040*
NL	0.301	0.091	0.010*	0.216	0.047	0.074*	0.246	0.061	0.025*
TU	0.444	0.197	<0.001*	0.258	0.067	0.036*	0.261	0.068	0.044*
TL	0.480	0.230	<0.001*	0.188	0.035	0.014*	0.283	0.080	0.011*

The sr was determined in multiple linear regression models controlling for the effects of age, sex, axial length, IOP, and SSI.
* Statistically significant values for $P < 0.05$.

in five sectors. In the meantime, the cpVD of all sectors were significantly associated with the corresponding VF MS and RNFLT in POAG eyes, respectively.

Overall, relationships between vascular and function characteristics were stronger than structure and function characteristics in both groups, which result was consistent with that of a previous study performed with POAG eyes.[11] This stronger relationship between vascular and function characteristics may be because vascular flow is reduced in eyes with sick or damaged ganglion cells, even before obvious RNFLT reduction. In a previous publication,[15] RNFLT and macular ganglion cell thicknesses were not different between APAC eyes and fellow PACS eyes, although VF sensitivity was substantially worse in APAC eyes. That result implied that reduction of VD may not be the only consequence of RNFL thinning in PACG eyes. Although we excluded the APAC eyes, most PACG participants experienced chronic higher IOP than POAG participants.[14] When we explored the factors associated with cpVD, both greater IOP and lower RNFLT were associated with lower cpVD in PACG eyes while only lower RNFLT showed significant relationship with lower cpVD. This result can be explained by the different pathogenic mechanisms of these two conditions.[13,23] PACG is characterized by uncontrolled IOP due to the mechanical obstruction of aqueous outflow, caused by the contact of the peripheral iris and the trabecular meshwork. On the other hand, although IOP is considered to be among the main risk factors for POAG, other factors may contribute to glaucomatous damage in POAG, especially in Asian populations where normal-tension glaucoma predominates.[24,25] Elevated IOP per se may primarily affect the retinal circulation as a whole, which may induce generalized reduction of cpVD and RNFLT in PACG eyes. On the other hand, reduction of cpVD may be a secondary change as

Table 3. Univariable and Multivariable Regression Analysis to Determine the Factors Associated With cpVD (%)

	Univariable			Multivariable		
Groups	**B**	**95% CI**	***P* Value**	**B**	**95% CI**	***P* Value**
PACG						
Age, y	−0.044	−0.277 to 0.189	0.705			
Sex	−5.933	−9.964 to −1.901	0.005*			
IOP, mm Hg	−0.480	−0.836 to −0.125	0.009*	−0.326	−0.524 to −0.129	0.002*
SSI	0.249	0.055 to 0.443	0.013*			
AL, mm	−2.598	−5.509 to 0.313	0.079			
RNFLT, μm	0.490	0.398 to 0.582	<0.001*	0.473	0.389 to 0.558	<0.001*
POAG						
Age, y	−0.143	−0.252 to −0.035	0.010*			
Sex	−4.010	−6.312 to −1.707	0.001*			
IOP, mm Hg	−0.186	−0.517 to 0.145	0.268			
SSI	0.066	−0.055 to 0.183	0.271			
AL, mm	−0.196	−1.265 to 0.872	0.715			
RNFLT, μm	0.345	0.259 to 0.431	<0.001*	0.345	0.259 to 0.431	<0.001*

CI, confidence interval.
* Statistically significant values for $P < 0.05$.

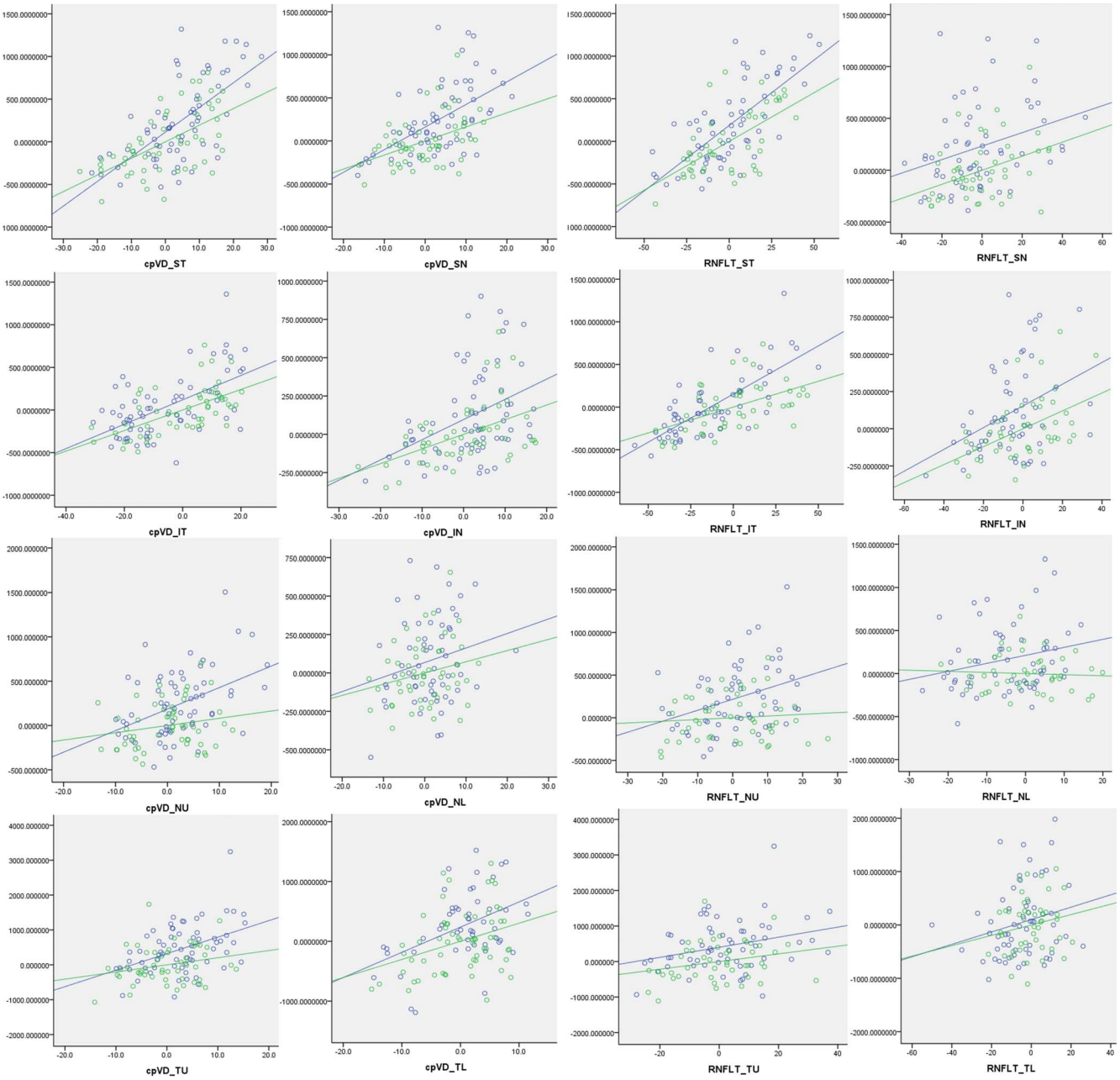

Figure 2. Partial residual plots showing the relationship between cpVD (%) or RNFLT (μm), and VFMS (1/L), controlling for the effects of other variables. In a partial residual plot, the *squares line* through the plotted points is shown. Dependent variable: VFMS values of corresponding sectors. Independent variable labeled in each plot. The other variables included age, sex, axial length, and cpVD or RNFLT. *Blue dots* indicate POAG eyes and *green dots* indicate PACG eyes.

consequence of RNFL reduction in POAG eyes as shown by linear regression analysis, which demonstrated that lower RNFLT was the only factor associated with lower cpVD. Nouri-Mahdavi et al.[23] showed that the pattern of glaucomatous damage of PACG was different with POAG.[23] In the current study, POAG eyes had a higher PSD than that in PACG eyes for given MD values, which suggested more localized patterns of loss in POAG eyes compared with PACG eyes and more diffuse VF damage in PACG eyes compared with POAG eyes. This finding is in line with other previous studies.[26–29] Therefore, it can be postulated that increased IOP in PACG can result in reduction of cpVD, while a reduction of vasculature was accompanied by loss of RNFL in POAG. Further longitudinal studies with a larger sample size regarding progressive vascular changes in these two disease categories are warranted to confirm this speculation.

The limitations of this study are as follows. The number of enrolled eyes was relatively small, and the subjects were all Korean. Hence, our outcome may not be generalizable to other races and to the general population with PACG. Since eyes with APAC were relatively few and the time of OCTA imaging, which may affect RNFLT and cpVD, was variable among those patients, we excluded those acute attack eyes. If the sample size could be enlarged, subgroup analysis of acute attack eyes may yield insight into the ischemic effect of IOP elevation per se. The cross-sectional design of the present study was another limitation. Further longitudinal studies are necessary to determine the cause-and-effect relationship between structural

characteristics, vascular factors, and functional damage. Finally, OCTA measures VD, not the retinal circulation itself. Hence, our result on the vascular–function relationship should be interpreted with caution in this context.

In conclusion, POAG and PACG eyes showed a different vascular–function relationship when determined by OCTA. Further, factors associated with reduced cpVD were different between POAG and PACG groups. The cpVD showed a better correlation with VFMS than did RNFLT in PACG eyes. This suggests that cpVD may be a potential biomarker for the assessment of glaucomatous functional damage in PACG eyes.

Acknowledgments

Supported by a grant (2018-0303) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, South Korea, and by the Basic Science Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Education, Science, and Technology (No. NRF-2017R1A2B4007792).

Disclosure: **Y.H. Jo**, None; **K.R. Sung**, None; **S.-C. Yun**, None

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