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Glaucoma

The Inter-Eye Differences of the Circumpapillary Microvasculature in Primary Open-Angle Glaucoma

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Purpose: To assess inter-eye differences of circumpapillary vessel density (cpVD) in patients with primary open-angle glaucoma (POAG) and elucidate factors implicated in glaucomatous vascular pathology.

Methods: POAG subjects and controls underwent optical coherence tomography (OCT) and OCT angiography (OCTA) imaging in both eyes. Inter-eye differences of OCT, OCTA, visual field (VF) and other ophthalmic parameters were assessed.

Results: Seventy-two POAG subjects and 53 controls were similar in age, gender, and visual acuity ($P \geq 0.28$ for all). POAG subjects had greater retinal nerve fiber layer (RNFL) asymmetry than controls (10 ± 10 µm vs. 5 ± 5 µm, $P < 0.001$). POAG patients also demonstrated significantly asymmetric mean deviation (MD) between the worse (−5.2 ± 4.0 dB) and better eye (−1.5 ± 2.6 dB, $P < 0.001$). However, POAG subjects had similar inter-eye cpVD asymmetry compared to controls (3.5% ± 2.6% vs. 3.1% ± 1.9%, respectively; $P = 0.32$). In a multivariable regression, MD asymmetry was associated with greater RNFL asymmetry ($\beta = 0.540$; 95% confidence interval [CI], 0.249–0.830; $P < 0.001$), whereas treated systemic hypertension ($\beta = -0.415$; 95% CI, −0.679 to −0.151; $P < 0.001$) was associated with decreased cpVD asymmetry in POAG subjects.

Conclusions: POAG subjects demonstrated greater inter-eye RNFL asymmetry than controls, but similar cpVD asymmetry. Although RNFL asymmetry was associated with difference in VF, inter-eye difference of circumpapillary microvasculature was minimized by systemic hypertension treatment, supporting systemic determinants of glaucomatous vascular pathology.

Translational Relevance: Our findings highlight a discordance in vascular pathology and structural RNFL damage between eyes in POAG, suggesting a systemic predisposition of vascular pathology in POAG.

Introduction

Primary open-angle glaucoma (POAG) is a chronic, progressive, and irreversible optic neuropathy characterized by optic nerve head (ONH) changes, retinal ganglion cell loss, and permanent visual field (VF) loss.[1] Although the disease is usually bilateral, clinical asymmetry is common, with one eye developing damage before the other.[1–3] Inter-eye asymmetry of the retinal nerve fiber layer (RNFL), VF deficit, and cup-to-disc ratio (CDR) has strong associations with POAG, particularly in early stages of the disease.[4–8] However, multiple systemic diseases are also implicated in POAG, including cardiovascular and inflammatory diseases.[6,9–11]

An important area of research in glaucoma disease pathogenesis is the vascular etiology, which hypothesizes that impaired optic nerve perfusion results in retinal ganglion cell death.[12] Optical coherence

tomography angiography (OCTA) is an emerging non-invasive technology that has facilitated further investigations into this area. Prior studies have shown a reduction of superficial vessel density in the circumpapillary region of the ONH (cpVD) that correlates with glaucoma severity, VF loss, and history of disc hemorrhage.[13–15] However, whether vascular compromise affects both eyes symmetrically in glaucoma has not been fully explored. Beyond glaucoma, systemic vascular parameters such as hypertension show correlation with OCTA measurements.[16–18] The association between glaucoma and vasospastic conditions such as Raynaud's syndrome and migraines further suggests a systemic vascular contribution towards POAG.[19] Patients with POAG demonstrate microvascular alterations in both the ONH and the nailbeds of their fingers, suggesting that this pathogenic process extends beyond the diseased eye(s).[20] Given the association of ophthalmic vasculature with systemic factors, the inter-eye relationship of vascular parameters likely differs from that of structural parameters in POAG. Few studies have investigated the inter-eye relationship of OCTA parameters, which would provide insight into ophthalmic and systemic regulators of vascular damage in POAG.

In this study, we assess inter-eye differences in the circumpapillary vessel density among POAG subjects and controls. We hypothesize that glaucomatous vascular pathology is likely impacted by systemic parameters and may not manifest with inter-eye asymmetry as seen with VF testing and structural RNFL. We also assess whether ophthalmic and systemic factors are associated with inter-eye asymmetry of structural and vascular parameters. From these analyses, we aim to shed light on the nature of vascular compromise in POAG.

Methods

This cross-sectional study was approved by the Mass General Brigham Institutional Review Board, complied with Health Insurance Portability and Accountability Act regulations, and adhered to the tenets set forth by the Declaration of Helsinki. Written informed consent was obtained from all study subjects.

Study Population

POAG subjects and controls were recruited from the glaucoma and comprehensive ophthalmology service at Massachusetts Eye and Ear, respectively. Inclusion criteria for all subjects were age between 35 and 90 years and best corrected visual acuity (BCVA) 20/40 or better. Exclusion criteria were refractive error of more than 6.0 diopters (D) or less than −6.0 D, greater than 3.0 D astigmatism, significant retinal pathology affecting BCVA or VF testing, and other non-glaucomatous optic neuropathies.

Additional inclusion criteria for POAG subjects were open angle on gonioscopy, RNFL thinning on OCT, and a corresponding characteristic glaucomatous VF defect.[21] POAG subjects were excluded if they had secondary open-angle glaucoma, prior penetrating glaucoma surgeries or significant optic disc torsion, defined as longest axis rotation of $\geq 15°$ outside the vertical meridian or tilt ratio between the shortest and longest disc diameter of <0.75.[22–24] Additional exclusion criteria for controls were examination findings suggestive of glaucoma including CDR asymmetry greater than 0.2 or CDR 0.6 or greater in either eye, a diagnosis of glaucoma suspect, or a family history of glaucoma. Demographic and ocular data were obtained from the electronic health record. POAG subjects were further stratified into normal tension glaucoma (NTG) and high-tension glaucoma (HTG) subtypes based on maximum intraocular pressure (Tmax) records of the eye with worse VF mean deviation (MD). HTG was defined as having Tmax $>$ 21 mm Hg whereas NTG was defined as Tmax $<$ 21 mm Hg.[25,26]

Imaging Protocol and Analysis

All subjects underwent pharmacologic pupil dilation and imaging of both eyes in random order. Imaging was obtained using a swept-source OCT (SS-OCT) device (Triton; Topcon, Tokyo, Japan) operated by either imaging technicians or research staff. Retinal nerve fiber layer thickness (RNFLT) measurements were automatically generated by the device from a 6-mm three-dimensional cube scan of the ONH. *En face* OCTA images were obtained over 4.5 × 4.5-mm fields centered over the ONH and segmented from the internal limiting membrane to the posterior RNFL boundary. OCT scans and OCTA images of both eyes from the same day and of adequate image quality were included for analysis. Adequate image quality was defined as having image quality score (IQS) $\geq$ 45 for structural OCT and $\geq$ 40 for OCTA, as well as absence of artifacts in the scanning circle.[27,28]

SS-OCT OCTA image analysis was performed using customized plugins on ImageJ Fiji (National Institutes of Health, Bethesda, MD, USA) by two readers (J.A.S. and G.E.J.) using published protocols previously described in the literature.[21,29] The readers performed analyses independently and were masked to the diagnosis. To briefly summarize, the circum-

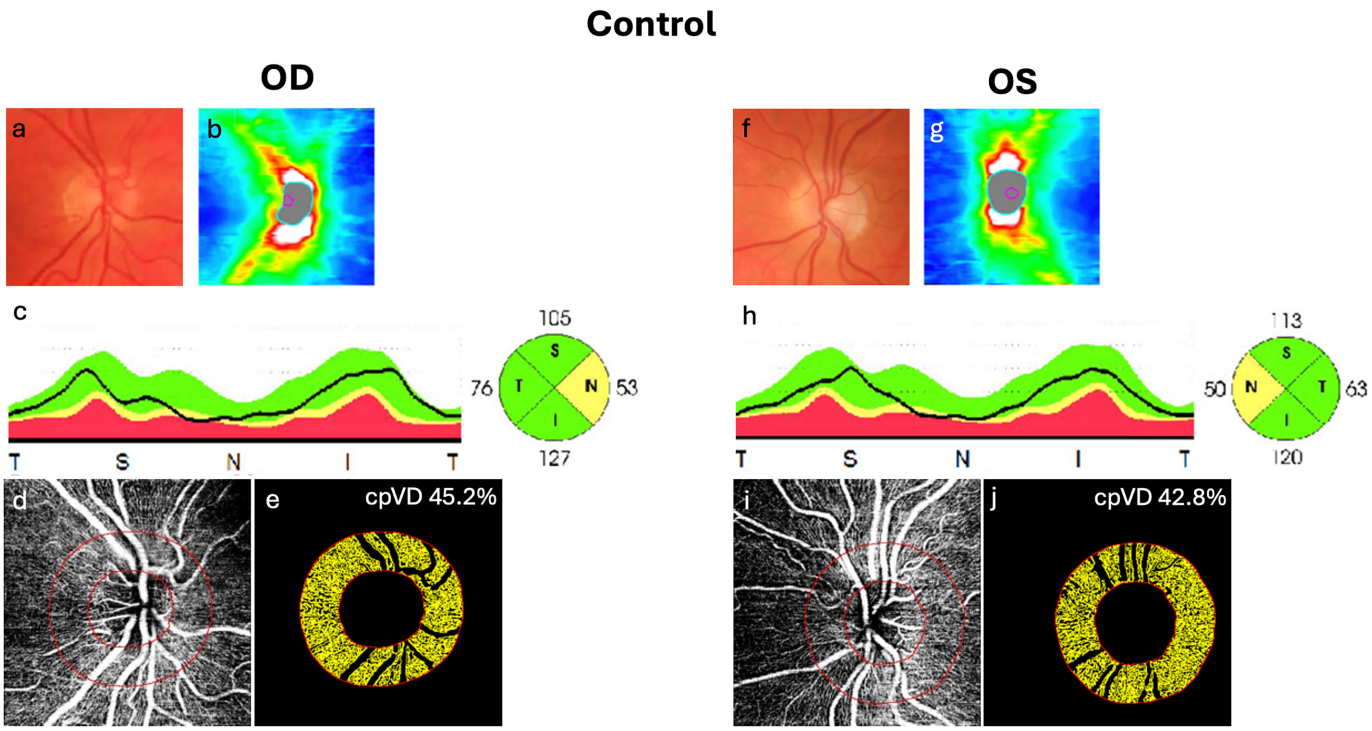

Figure 1. Fundus photos, OCT, and OCTA from both eyes of an example control subject. The subject was a 70-year-old White female without POAG. CDR was 0.3 in both eyes (**a**, **f**). OCT showed healthy RNFL bilaterally (90 µm OD and 86 µm OS) with RNFLT asymmetry of 4 µm (**b**, **c**, **g**, **h**). The circumpapillary region is a 0.7mm annulus from Bruch's membrane opening (*red outlines*) and delineated on the superficial OCTA image centered on the optic nerve (**d**, **i**). After large vessel removal, cpVD measurement is obtained by selecting the microvasculature (*yellow*) with a thresholding method and dividing the area occupied by the microvasculature over the entire circumpapillary region not including large vessels and found to be 45.2% for OD and 42.8% for OS (**e**, **j**). For the control subject, the cpVD inter-eye asymmetry was 2.4%. OD, oculus dexter; OS, oculus sinister.

papillary region was defined as a 0.7-mm annulus around Bruch's membrane opening and large vessels within this region were excluded automatically using customized software (Figs. 1; 2). CpVD was measured as the percentage area occupied by the microvasculature selected by a thresholding method. Measurements between readers for each eye were averaged for analysis.

A subset of study subjects also underwent structural and vascular imaging on a spectral-domain OCT (SD-OCT) device (Optovue, Inc, Fremont, CA, USA), which had become available later in the recruitment phase of this research study. *En face* circumpapillary scans were obtained over 4.5 × 4.5-mm fields centered over the ONH, and macula scans were obtained over 6 × 6-mm fields centered over the fovea. Adequate image quality was defined as having signal strength ≥ 5 and signal strength index ≥ 48, as well as absence of artifacts in the image.[30,31] The SD-OCT device software (Software version 2018.1.1.85; Visionix USA, Lombard, IL, USA) automatically calculates OCTA-based parameters and OCT-based thickness from the same scans.

Visual Field Measurements

Reliable Humphrey VF testing (Humphrey Visual Field perimeter; Carl Zeiss Meditec, Dublin, CA, USA) on the Swedish Interactive Thresholding Algorithm standard 24-2 algorithm was obtained from the clinic visit nearest in time to the OCTA imaging for all POAG subjects. Reliable testing was defined as having fixation losses ≤ 33%, and false-positive and false-negative rates of ≤ 20%.[32,33] If one eye had unreliable testing on that day, the next VF nearest to the time of OCTA imaging was evaluated if the time difference between VF and OCT testing was within six months. POAG disease severity was determined based on the eye with worse MD, with mild disease defined as MD ≥−6 decibels (dB), and moderate-to-severe disease defined as MD <−6 dB.[34,35]

Primary and Secondary Outcome Measures

Our primary outcome measures included (1) inter-eye asymmetry, defined as the absolute difference between eyes or |OD – OS|, of OCT and OCTA param-

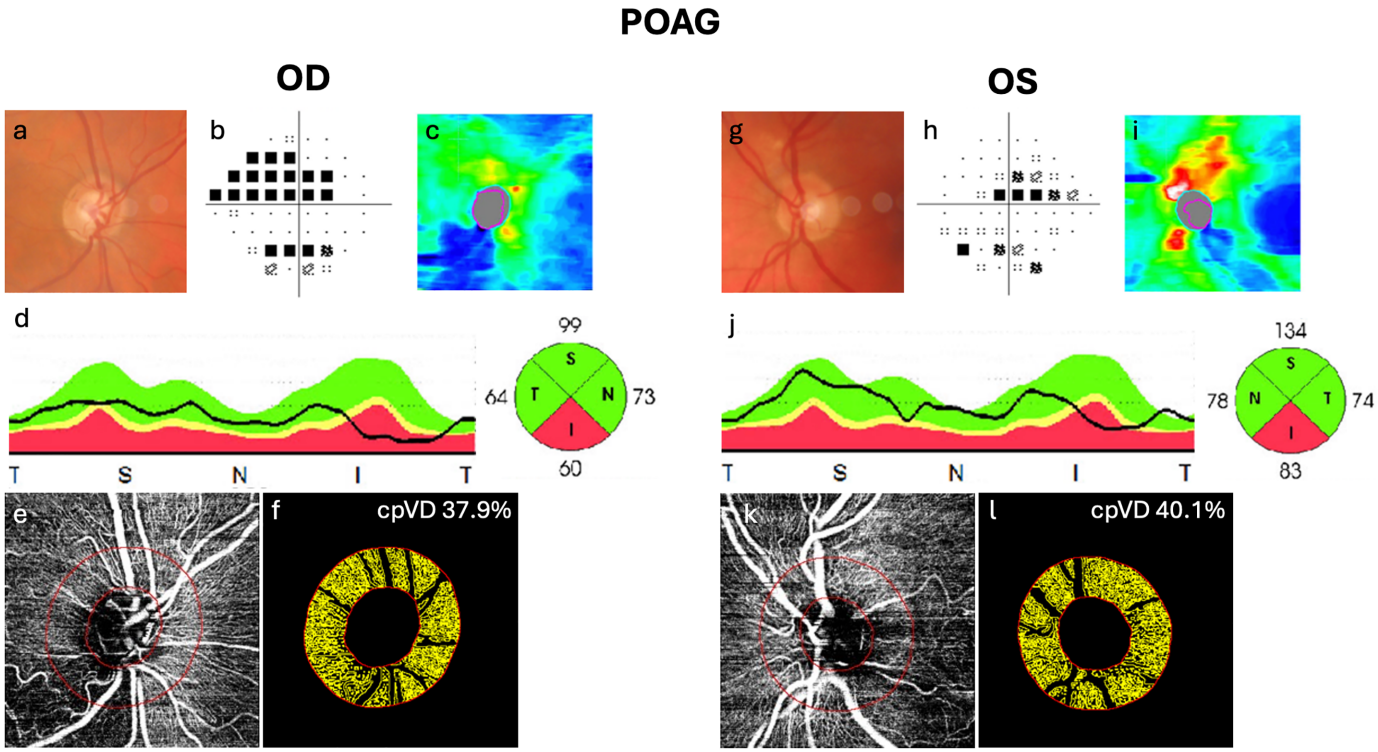

Figure 2. Fundus photos, OCT, available VF testing, and OCTA from both eyes of an example POAG subject. The subject was a 75-year-old White female with history of POAG in both eyes. CDR was 0.8 for OD and 0.6 for OS (**a**, **g**). On VF testing, there was superior hemifield loss and an inferior arcuate loss for OD (**b**), whereas there was early superior paracentral loss and inferior arcuate loss for OS (**h**). MD was measured as −8.58 dB for OD and 0.38 dB for OS, with MD inter-eye asymmetry of 9 dB. OCT showed inferior RNFL thinning in both eyes (average RNFLT 74 µm OD and 92 µm OS) with RNFLT asymmetry of 18 µm (**c**, **d**, **i**, **j**). The circumpapillary OCTA is a 0.7 mm annulus from Bruch's membrane opening (*red outlines*) on the superficial OCTA image centered on the optic nerve, and demonstrated inferotemporal microvascular loss in both eyes (**e**, **k**). After large vessel removal, cpVD was found to be 37.9% for OD and 40.1% for OS (**f**, **l**). For the POAG subject, the cpVD inter-eye asymmetry was 2.2%. POAG, primary open angle glaucoma.

eters among POAG subjects and healthy controls and (2) systemic and ophthalmic factors associated with RNFLT and cpVD asymmetry in POAG subjects. This definition of asymmetry parallels prior studies on inter-eye asymmetry, allowing for better contextualization of findings while also allowing the analyses to focus on factors influencing the magnitude of asymmetry rather than directionality.[4,36,37]

Our secondary outcome measures included subgroup comparisons of inter-eye asymmetry based on glaucoma severity as well as NTG verses HTG subtype. Linear regressions were additionally performed between asymmetry parameters and VF MD. To factor in directionality based on the presumption of worse disease corresponding to worse damage, we also repeated our primary comparisons by defining asymmetry as the difference of [worse eye − better eye] based on visual field MD for POAG subjects, while using the difference of [OD − OS] for healthy controls.

Statistical Analysis

Statistical analyses were conducted with commercially available software (Stata version 16.0; StataCorp, College Station, TX, USA) and R statistical package version 4.4.1 (available at https://www.r-project.org; assessed June 14, 2024). The χ^2 and two-tailed *t*-tests were used to compare normally distributed categorical variables and continuous variables, respectively. Variance was assessed to determine whether Welch's *t*-tests should be applied. Kruskal Wallis test was used to compare asymmetry between controls, NTG, and HTG, as well as between controls, mild POAG, and moderate-to-severe POAG. Dunn's pairwise test was used for pairwise comparisons. The Benjamini-Hochberg false discovery rate method for *P*-value adjustment was used to control for multiple comparisons. After the completion of data collection and analysis, a post hoc power analysis was used to assess the statistical power of the study to detect a clinically significant effect size based on prior literature.

The impact of systemic and ophthalmic variables on RNFLT asymmetry and cpVD asymmetry were assessed in a multivariable linear regression analysis after logarithmic transformation of all the asymmetry parameters to address data skewness.[38] Systemic

predictors included age, gender, race, treated hypertension, and diabetes. Ophthalmic predictors included moderate-to-severe glaucoma, MD asymmetry, intraocular pressure (IOP) asymmetry, central corneal thickness (CCT) asymmetry, maximum IOP (Tmax) asymmetry, documented history of disc hemorrhage, and asymmetry of IQS, which measures imaging quality of OCT or OCTA. Additionally, cpVD asymmetry was included in the multivariable analysis for RNFLT asymmetry and RNFLT asymmetry was included in the multivariable analysis for cpVD asymmetry. Additional multivariable analyses were performed without logarithmic transformation and with stepwise selection based on R^2 criteria to confirm the results.

Results

Patient Characteristics

Seventy-two POAG subjects and 53 healthy controls were included. The groups were similar in age (mean ± standard deviation [SD] 68 ± 10 years among POAG vs. 66 ± 9 years among controls, $P = 0.28$; Table 1). The groups were also similar in terms of gender distribution

Table 1. Demographic and Ophthalmic Characteristics of POAG and Control Subjects

	Control ($n = 53$)	POAG ($n = 72$)	*P*-Value
Demographic parameters			
Age (years)	66 ± 9	68 ± 10	0.28
Sex (Female)	59%	60%	0.89
Race (White)	98%	82%	**0.005**
Ethnicity (Hispanic)	2%	1%	0.83
Diabetes mellitus	2%	11%	0.05
Hypertension[a]	45%	32%	0.14
Treated	41%	28%	0.13
Untreated	4%	4%	>0.99
Ocular parameters			
BCVA (logMAR)	0.08 ± 0.12	0.09 ± 0.11	0.47
CCT (µm)	N/A	541 ± 39	
IOP (mm Hg)[b]	15 ± 2	14 ± 4	**0.005**
Tmax (mm Hg)[c]	17 ± 3	22 ± 6	**<0.001**
Worse eye		22 ± 6	
Better eye		22 ± 5	
VF MD (dB)	N/A	−3.3 ± 3.8	
Worse eye[d]		−5.2 ± 4.0	
Better eye[d]		−1.5 ± 2.6	
Disc hemorrhage	N/A	33%	
Worse eye only[d]		11%	
Better eye only[d]		18%	
Both eyes		4	
CDR	0.3 ± 0.1	0.7 ± 0.1	**<0.001**
RNFLT (µm)[e]	102 ± 11	78 ± 13	**<0.001**
cpVD (%)	41 ± 4	38 ± 4	**<0.001**
Image quality score			
OCTA	70 ± 6	68 ± 7	**0.006**
OCT[e]	64 ± 7	63 ± 7	**0.04**

Significant *P*-values at level $p < 0.05$ are bolded.
[a]Treatment of hypertension was defined as being on anti-hypertensive medications at the time of imaging.
[b]Not available for 10 eyes of five POAG subjects.
[c]Not available in 12 eyes of six POAG subjects.
[d]Statistically significant difference ($P < 0.001$) between worse and better eye at significance level $P < 0.05$.
[e]Not available from four eyes of two control subjects.

Table 2. Inter-Eye Asymmetry of SS-OCT Ophthalmic Parameters in POAG Subjects and Healthy Controls

Parameter	Control ($n = 53$)	POAG ($n = 72$)	*P*-Value
RNFLT asymmetry (μm)[a]	5 ± 5 (95% CI, 3.8 to 6.8)	10 ± 10 (95% CI, 7.8 to 12.1)	**<0.001**
CpVD asymmetry (%)	3.1 ± 1.9 (95% CI, 2.6 to 3.9)	3.5 ± 2.6 (95% CI, 2.9 to 4.1)	0.32
Other ophthalmic parameters			
VF MD asymmetry (dB)	N/A	3.7 ± 2.9	
CCT asymmetry (μm)	N/A	8 ± 8	
IOP asymmetry (mm Hg)[b]	1 ± 1	1 ± 2	0.05
Tmax asymmetry (mm Hg)[c]	1 ± 1	2 ± 2	**0.01**
CDR asymmetry	0.0 ± 0.1	0.1 ± 0.1	**<0.001**

Significant *P*-values at level $P < 0.05$ are bolded.
[a]Not available for two control subjects.
[b]Not available for five POAG subjects.
[c]Not available in six POAG subjects.

(60% vs. 59% female, $P = 0.89$), although more controls were White compared to POAG subjects (98% vs. 82% White, $P = 0.005$). Prevalence of diabetes mellitus and systemic hypertension did not differ between the groups (11% vs. 2% for POAG subjects and controls, respectively; $P = 0.05$; 32% vs. 45% for POAG subjects and controls, respectively; $P = 0.14$). Twenty-eight percent of POAG subjects and 41% of controls were on antihypertensive medications ($P = 0.13$).

POAG subjects and controls had similar average BCVA at the time of imaging (logMAR 0.09 ± 0.11 vs. 0.08 ± 0.12, respectively; $P = 0.47$; Table 1). POAG subjects had larger average CDR (0.7 ± 0.1 vs. 0.3 ± 0.1, $P < 0.001$), higher Tmax (22 ± 6 vs. 17 ± 3 mm Hg, $P < 0.001$), and lower average IOP on the day of imaging (14 ± 4 vs. 15 ± 2 mm Hg, $P < 0.001$) compared to controls. POAG eyes had an average CCT of 541 ± 39 μm and an average VF MD of −3.3 ± 3.8 dB. Thirty-three percent of POAG subjects had a history of disc hemorrhage; 11% had disc hemorrhage noted in the worse eye, 18% had disc hemorrhage in the better eye, and 4% had a history of disc hemorrhage in both eyes.

OCT and OCTA imaging from both eyes in POAG subjects had lower IQS compared to those from controls (63 ± 7 vs. 64 ± 7, $P = 0.04$; 68 ± 7 vs. 70 ± 6, $P = 0.006$, respectively; Table 1). Regarding structural OCT, POAG eyes demonstrated thinner average RNFLT compared to controls (78 ± 13 μm vs. 102 ± 11 μm, $P < 0.001$). Inter-reader agreement for cpVD was excellent with an intraclass correlation coefficient of 0.953. POAG eyes had decreased average cpVD (38% ± 4% vs. 41% ± 4%, $P < 0.001$) compared with control eyes (Table 1). A subgroup analysis was performed involving only White subjects because of differences in racial distribution between the study groups[39] (see Supplementary Table S1 for subgroup analysis of White subjects). White POAG subjects demonstrated decreased average RNFLT and average cpVD compared with White healthy controls (77 ± 13 μm vs. 101 ± 11 μm, $P < 0.001$; 37% ± 4% vs. 41% ± 4%, $P < 0.001$).

Inter-Eye Differences

Table 2 summarizes the inter-eye differences of OCT and OCTA parameters among POAG subjects and healthy controls, which are visually represented in Figure 3. Visual field MD asymmetry among POAG subjects was 3.7 ± 2.9 dB (Table 2). There was a statistically significant difference between the MD of the better eye (−1.5 ± 2.6 dB) and worse eye (−5.2 ± 4.0 dB) among POAG subjects ($P < 0.001$). POAG subjects had greater inter-eye asymmetry of Tmax (2 ± 2 vs. 1 ± 1 mm Hg, $P = 0.01$) and CDR (0.1 ± 0.1 vs. 0.0 ± 0.1, $P < 0.001$) than control subjects.

Based on SS-OCT measurements, POAG subjects had significantly greater RNFLT asymmetry than control subjects (10 ± 10 μm vs. 5 ± 5 μm, $P < 0.001$; Table 2; Fig. 3). However, cpVD asymmetry did not differ between POAG subjects and controls (3.5% ± 2.6% vs. 3.1% ± 1.9%, $P = 0.32$). Among White subjects, there was a significant difference in RNFLT asymmetry in POAG subjects versus controls (10 ± 9 μm vs. 5 ± 5 μm, $P < 0.001$) but no statistically significant difference in cpVD asymmetry (3.4% ± 2.3% vs. 3.0% ± 1.9%, $P = 0.365$; Supplementary Table S1 for characteristics and inter-eye asymmetry of White subjects). In the post-hoc power analysis performed to assess the study's statistical power, a clinically significant effect size of cpVD asymmetry was estimated as 2.0% based on previous reported effect sizes.[36,37] Using this clinically significant effect size and the sample size of our study resulted in a statistical power of 0.99,

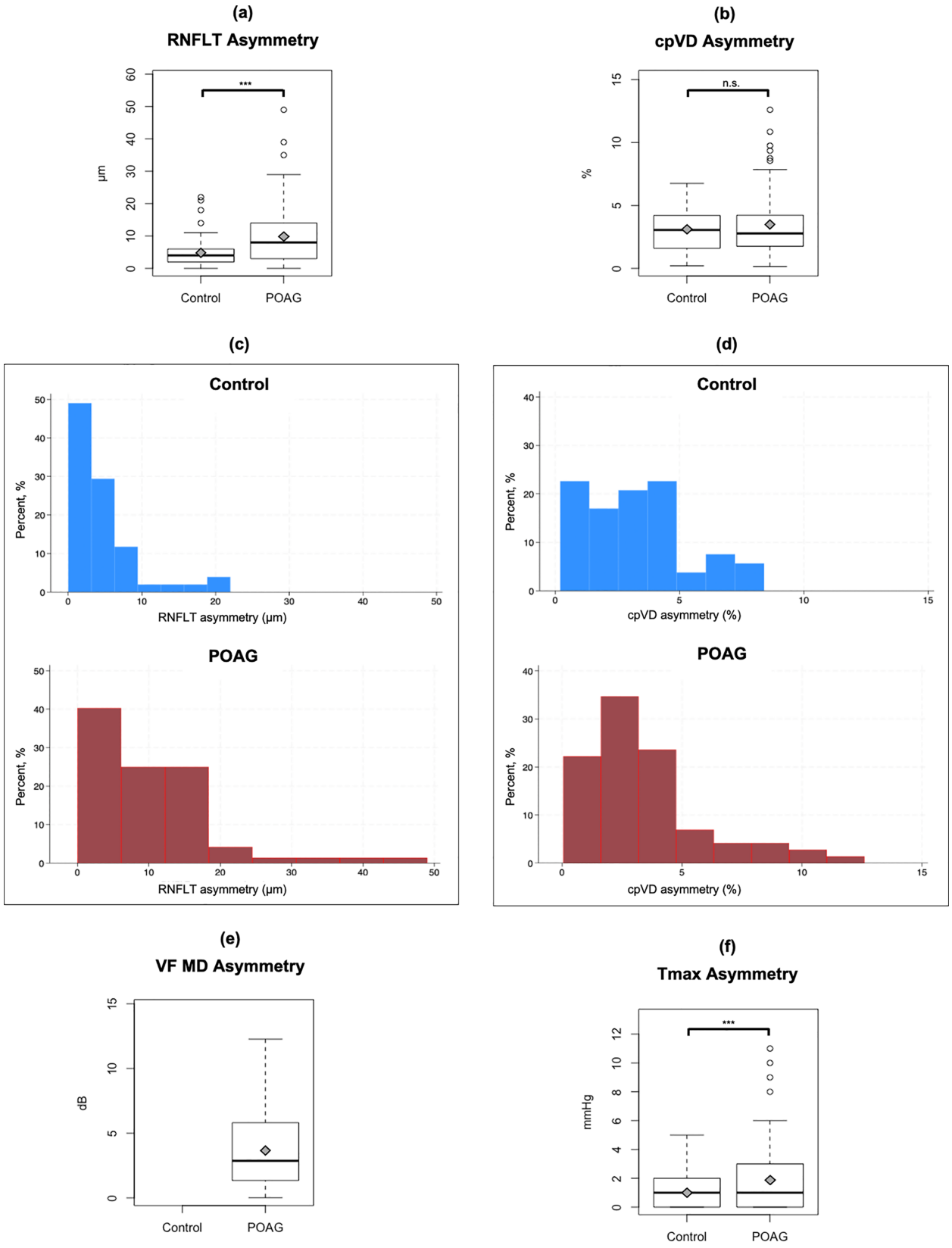

Figure 3. Box plots and histogram plots showing asymmetry of ophthalmic parameters between control and POAG subjects. POAG subjects showed greater inter-eye asymmetry compared to controls in RNFL asymmetry (**a**), Tmax asymmetry (**f**), but not in cpVD asymmetry (**b**). VF MD was not available for control subjects (**e**). Histogram plots for each respective group are shown for RNFLT asymmetry (**c**) and cpVD asymmetry (**d**). ***$P < 0.05$. Mean represented by *gray diamond*. cpVD, circumpapillary vessel density; MD, mean deviation; n.s., not significant; RNFL, retinal nerve fiber layer; Tmax, maximum intraocular pressure; VF, visual field.

Table 3. Inter-Eye Asymmetry of Parameters in POAG Subjects and Healthy Controls With SD-OCT and SS-OCT OCTA Imaging

Peripapillary parameter	Control, $n = 20$	POAG, $n = 26$	*P*-Value[a]
SD-OCT			
RNFLT (µm)	4 ± 4	10 ± 8	**0.007**
CpVD			
Small vessels	2.8% ± 1.8%	4.4% ± 3.1%	0.100
All vessels	2.8% ± 1.8%	4.1% ± 3.2%	0.283
SS-OCT			
RNFLT (µm)[b]	4 ± 4	10 ± 8	**0.003**
CpVD	3.3% ± 2.2%	3.4% ± 2.2%	0.964
Other ocular parameters			
VF MD (dB)	N/A	3.5 ± 2.8	
CCT (µm)	N/A	6 ± 5	
IOP (mm Hg)[c]	1 ± 1	1 ± 1	0.981
Tmax (mm Hg)	1 ± 1	2 ± 2	0.126
CDR	0 ± 0.1	0.1 ± 0.1	**<0.001**
Macular Parameter	**Control, $n = 20$**	**POAG, $n = 21$**	***P*-Value**
GCC thickness (µm)			
Foveal	4 ± 8	7 ± 6	**0.030**
Parafoveal	2 ± 3	12 ± 10	**<0.001**
Perifoveal	3 ± 3	8 ± 7	**0.003**
Superficial VD			
Whole-image	2.5% ± 1.6%	3.2% ± 3.1%	0.985
Fovea	5.5% ± 4.8%	5.4% ± 6.4%	0.666
FD 300[d]	3.6% ± 2.6%	5.5% ± 4.6%	0.361
Parafovea	3.2% ± 3.0%	3.7% ± 3.0%	0.426
Perifovea	2.9% ± 1.7%	3.6% ± 2.0%	0.995
FAZ area (mm^2)[e]	0.1% ± 0.1%	0.1% ± 0.4%	0.129
Other ocular parameters			
VF MD (dB)	N/A	3.8 ± 3.3	
CCT (µm)	N/A	8 ± 8	
IOP (mm Hg)	1 ± 1	1 ± 1	0.891
Tmax (mm Hg)	1 ± 1	1 ± 1	0.514
CDR	0 ± 0.1	0.1 ± 0.1	**<0.001**

Significant *P*-values at level $P < 0.05$ are bolded.
[a]Calculated using Mann Whitney U tests.
[b]Not available for one control subject.
[c]Not available for three POAG subjects.
[d]Not available for one control subject.
[e]Not available for one control subject.

which corresponds to a 99% probability of detecting a clinically significant difference in cpVD inter-eye asymmetry between POAG and controls.

Twenty-six POAG subjects and 20 controls underwent additional imaging on a SD-OCT device (Table 3). The POAG subgroup had VF MD asymmetry of 3.5 ± 2.8 dB showing significant difference in VF MD between the worse eye and the better eye ($P < 0.001$). The POAG subgroup demonstrated greater RNFLT asymmetry than the controls (10 ± 8 µm vs. 4 ± 4 µm, $P = 0.007$). Similar to the findings from the SS-OCT device, cpVD asymmetry calculated from this device

did not statistically differ between groups whether it was measured with large vessels included ($P = 0.28$) or excluded ($P = 0.10$). Macular imaging also demonstrated significantly greater structural differences in GCC thickness in the foveal, parafoveal, and perifoveal regions ($P \leq 0.03$) in the POAG group ($n = 21$) compared to controls ($n = 20$), whereas macular superficial vessel density (VD) asymmetry did not statistically differ between groups in any region ($P \geq 0.361$).

Comparisons factoring in the worse versus better eye among the POAG subjects also demonstrated significantly greater RNFLT asymmetry compared to healthy controls (-7.83 ± 11.13 µm vs. 0.02 ± 6.84 µm, $P < 0.001$), whereas there was no statistically significant difference in cpVD asymmetry between the groups ($-1.59\% \pm 4.05\%$ vs. $-0.44\% \pm 3.94\%$, $P = 0.11$; Supplementary Table S2 and Supplementary Fig. S1).

Inter-Eye Differences Based on IOP or Glaucoma Severity

Inter-eye differences were further assessed based on available maximum IOP in the eye with worse MD. Thirty-two NTG subjects and 34 HTG subjects in the POAG group were included (See Supplementary Table S3 for inter-eye analysis based on history of NTG or HTG). With this stratification, RNFLT asymmetry was higher among NTG subjects compared to controls (10 ± 8 µm vs. 5 ± 5 µm, $P = 0.002$) and higher among HTG subjects compared to controls (11 ± 11 µm vs. 5 ± 5 µm, $P < 0.001$). NTG and HTG subjects shared similar RNFLT asymmetry (10 ± 8 µm vs. 11 ± 11 µm, $P = 0.242$). No significant differences in cpVD asymmetry were detected between controls, NTG subjects, and HTG subjects ($P = 0.777$).

Inter-eye differences were also assessed based on glaucoma severity (See Supplementary Table S4 for inter-eye analysis based on glaucoma severity). RNFLT asymmetry was higher in mild POAG compared to controls (10 ± 11 µm vs. 5 ± 5 µm, $P = 0.007$) and higher in moderate-to-severe POAG compared to controls (10 ± 6 µm vs. 5 ± 5 µm, $P = 0.002$); the mild and moderate-to-severe POAG subgroups had similar RNFLT asymmetry (10 ± 11 µm vs. 10 ± 6 µm, $P = 0.244$). No significant differences in cpVD asymmetry were detected between controls, mild POAG subjects, and moderate-to-severe POAG subjects ($P = 0.531$).

The associations between VF MD of the worse eye and either RNFLT or cpVD asymmetry were not significant in the linear regression analysis, suggesting that worsening glaucoma did not meaningfully predict the degree of structural or microvascular asymmetry

Table 4. Multivariable Regression Analysis of Factors Associated With RNFLT Asymmetry Between Eyes in POAG Subjects After Log-Transformation of Asymmetry Data

	Univariable Analysis			Multivariable Analysis[a]		
RNFLT Asymmetry[b]	β	95% CI	*P*-Value	β	95% CI	*P*-Value
Systemic factors						
Age (years)	0.004	−0.014 to 0.022	0.667			
Gender (Female)	−0.078	−0.435 to 0.278	0.662			
Race (White)	−0.005	−0.450 to 0.460	0.982			
Treated Hypertension	−0.041	−0.335 to 0.416	0.828			
Diabetes Mellitus	−0.312	−0.864 to 0.241	0.264			
Ocular factors						
Moderate-to-severe glaucoma	0.155	−0.219 to 0.529	0.412			
MD asymmetry[b]	0.472	0.175 to 0.768	**0.002**	0.540	0.249 to 0.830	**<0.001**
CCT asymmetry[b]	0.013	−0.214 to 0.239	0.912			
IOP asymmetry[b]	0.023	−0.049 to 0.095	0.526			
Tmax asymmetry[b]	0.025	−0.107 to 0.157	0.710			
Disc hemorrhage in better eye	0.095	−0.390 to 0.582	0.696			
Disc hemorrhage in worse eye	0.126	−0.295 to 0.546	0.553			
cpVD asymmetry[b]	0.214	−0.094 to 0.521	0.171			
OCT IQS asymmetry[b]	0.248	−0.033 to 0.530	**0.083**	0.337	0.074 to 0.601	**0.013**

Significant *P*-values at level $P < 0.05$ are bolded.
[a]Variables in the univariable model with $P < 0.10$ were included in the multivariable model.
[b]Log transformation of asymmetry parameter performed to address data skewness.

($\beta = -0.214$; 95% CI, –0.767 to 0.339; $P = 0.44$; $\beta = -0.026$; 95% CI, –0.182 to 0.130; $P = 0.74$; See Supplementary Fig. S2 for linear regressions of RNFLT asymmetry and cpVD asymmetry with VF MD of the worse eye).

Multivariable Analysis

Sixty-two POAG subjects (86% of the total POAG group) with available CCT, IOP, and Tmax data were included in the multivariable analysis examining systemic and ophthalmic factors associated with RNFLT and cpVD asymmetry. Results from the multivariable regression analysis of factors associated with RNFLT asymmetry are shown in Table 4. Gender, race, hypertension, diabetes, moderate-to-severe glaucoma, IOP asymmetry, Tmax asymmetry, disc hemorrhage history, and cpVD asymmetry were not significantly associated with RNFLT asymmetry in the univariable analysis and therefore not included in the multivariable analysis ($P \geq 0.171$). In the multivariable analysis, VF MD asymmetry ($\beta = 0.540$; 95% CI, 0.249–0.830; $P < 0.001$), and IQS asymmetry ($\beta = 0.337$; 95% CI, 0.074–0.601; $P = 0.013$) were both associated with greater RNFLT asymmetry. Directionality of the associations among the POAG subjects were assessed: 76% of POAG subjects had thinner RNFLT in the eye with worse MD, and 58% of subjects had thinner RNFLT in the eye with lower IQS on OCT imaging. The association of MD asymmetry ($\beta = 1.53$; 95% CI, 0.58–2.49; $P = 0.003$) and IQS asymmetry ($\beta = 0.58$; 95% CI, 0.06–1.11; $P = 0.03$) with RNFLT asymmetry was confirmed in a separate model with stepwise selection (See Supplementary Tables S5 and S7 for stepwise selected model of factors associated with RNFLT asymmetry).

Table 5 shows the results from the multivariable regression analysis of factors associated with cpVD asymmetry. Notably, glaucoma severity, IOP asymmetry, MD asymmetry, and RNFLT asymmetry were not significant predictors in the univariable analysis ($P \geq 0.171$) and were selected out in the multivariable model. In the multivariable model, treated hypertension was associated with decreased cpVD asymmetry ($\beta = -0.415$; 95% CI, −0.679 to −0.151; $P < 0.001$). In other words, POAG subjects with treated hypertension were less likely to have asymmetry in cpVD. Disc hemorrhage in the worse eye ($\beta = 0.269$; 95% CI, −0.027 to 0.566; $P = 0.074$) showed trend toward increased cpVD asymmetry, although this association did not reach significance in the multivariable model. This significant association between treated hypertension and cpVD asymmetry ($\beta = -2.56$; 95% CI, −3.93

Table 5. Multivariate Regression Analysis of Factors Associated With CpVD Asymmetry Between Eyes in POAG Subjects After Log-Transformation of Asymmetry Data

	Univariable Analysis			Multivariable Analysis[a]		
CpVD asymmetry[b]	β	95% CI	*P*-Value	β	95% CI	*P*-Value
Systemic factors						
Age (years)	−0.006	−0.020 to 0.008	0.414			
Gender (Female)	0.091	−1.014 to 0.363	0.509			
Race (White)	−0.016	−0.364 to 0.332	0.927			
Treated hypertension	−0.434	−0.702 to −0.167	**0.002**	−0.415	−0.679 to −0.151	**<0.001**
Diabetes mellitus	−0.299	−0.719 to 0.120	0.159			
Ocular factors						
Moderate-to-severe glaucoma	0.186	−0.097 to 0.470	0.195			
MD asymmetry[b]	0.139	−0.101 to 0.379	0.253			
CCT asymmetry[b]	−0.020	−0.194 to 0.153	0.814			
IOP asymmetry[b]	0.001	−0.055 to 0.057	0.976			
Tmax asymmetry[b]	0.032	−0.069 to 0.133	0.525			
Disc hemorrhage in better eye	0.270	−0.096 to 0.647	0.145			
Disc hemorrhage in worse eye	0.306	−0.007 to 0.620	0.055	0.269	−0.027 to 0.566	0.074
RNFLT asymmetry[b]	0.125	−0.055 to 0.304	0.171			
OCTA IQS asymmetry[b]	−0.033	−0.229 to 0.163	0.739			

Significant *P*-values at level $P < 0.05$ are bolded.
[a]Variables in the univariable model with $P < 0.10$ were included in the multivariable model.
[b]Log transformation of asymmetry parameter performed to address data skewness.

to −1.20; $P < 0.001$) was confirmed in a separate model with stepwise selection (See Supplementary Tables S6 and S7 for stepwise selected model of factors associated with cpVD asymmetry).

Patient Examples

Ophthalmic testing from an example control and POAG subject are shown in Figures 1 and 2, respectively. A 70-year-old White female without glaucoma had CDR 0.3 bilaterally (Figs. 1a, 1f). Structural OCT demonstrated healthy RNFL bilaterally without evidence of glaucomatous thinning and with minimal RNFLT asymmetry (4 µm; Figs. 1b, 1c, 1g, 1h). On OCTA, cpVD asymmetry was 2.4% (Figs. 1e, 1j). The POAG subject was a 75-year-old White female with CDR of 0.8 in the right eye and 0.6 in the left eye (Figs. 2a, 2g). On VF testing, the patient had superior hemifield loss and an inferior arcuate loss in the right eye with a MD of −8.58 dB, whereas the left eye VF shows early superior paracentral loss and inferior arcuate loss with an MD of 0.38 dB (Figs. 2b, 2h). Inter-eye MD asymmetry was 9 dB. Structural OCT was notable for inferior RNFL thinning bilaterally that was more severe in the right eye, with an RNFL asymmetry of 18 µm (Figs. 2c, 2d, 2i, 2j). OCTA imaging demonstrated inferotemporal microvascular loss in both eyes (Figs. 2e, 2k). Despite significantly greater RNFL asymmetry than the control subject and significant functional difference between eyes, cpVD asymmetry was 2.2% (Figs. 2f, 2l).

Discussion

Few studies to date have examined the relationship of vascular compromise between eyes in glaucoma. This was a cross-sectional analysis of the inter-eye difference in circumpapillary microvasculature in subjects with POAG and healthy controls. POAG subjects demonstrated decreased average RNFLT and decreased average cpVD compared to controls. Furthermore, POAG subjects demonstrated significant functional and structural differences between eyes, yet similar inter-eye cpVD asymmetry as controls. The lack of inter-eye asymmetry in the microvasculature was confirmed in a subset of subjects imaged on a different device in both the peripapillary and macular regions. Intraocular pressure and severity of glaucoma did not have an effect on cpVD asymmetry. In the multivariable analyses, differences in MD and imaging IQS were correlated with RNFLT asymmetry, whereas cpVD asymmetry was associated with treated systemic hypertension. The overall decrease in the circumpapillary microvasculature in POAG compared to control subjects along with the lack of microvascular asymmetry in the presence of significant RNFL inter-eye asymmetry in POAG subjects suggests a systemic predisposition of vascular pathology in POAG, which may affect both eyes despite a varying degree of structural damage.

Our findings differed from two previous reports, which demonstrated significant difference in cpVD asymmetry between POAG and control subjects, although our post hoc power analysis indicates that the study sample size was sufficient to detect clinically meaningful vessel density asymmetry as reported by Hou et al.[36] and Xu et al.[37] In the study by Xu et al.,[37] the authors examined OCTA asymmetry in Chinese POAG subjects with greater functional asymmetry (MD difference 5.8 ± 6.3 dB) than our study group (MD difference 3.7 ± 2.9 dB) and found significantly higher cpVD asymmetry in the POAG group (6.4% ± 5.2%) compared to controls (2.2% ± 1.7%). Notably, Xu et al.[37] used a different imaging machine (RTVue-XR Avanti, Optovue Inc., Fremont, CA) that measured vessel density without exclusion of large-caliber vessels.[36] Given that arteriolar narrowing is common in glaucoma, their results may have been impacted by hemodynamic alterations of the large retinal vessels.[40,41] To address this difference in methodology, we analyzed a subset of participants who underwent OCTA imaging on the same device, which also did not show a significant difference in cpVD asymmetry between POAG and controls after large vessel exclusion (Table 3). Hou et al.[36] also assessed vessel density asymmetry without large vessel exclusion and found increased cpVD asymmetry between controls and patients with mild glaucoma (median [IQR] 1.7% [0.8%–2.6%] and 2.2% [1.3%–4.3%], respectively). Our estimates of cpVD asymmetry for our control and POAG groups are the first that excluded large vessels and lie between the respective estimates from these two prior studies. Given these differing findings, we believe that large vessel removal is important in future studies to detect changes in the circumpapillary microvasculature and assess for inter-eye asymmetry. To address the possibility that directionality may unmask greater differences in asymmetry, we also performed comparisons based on the worse eye relative to the better eye, which yielded similar results (Supplementary Table S2).

Overall, our findings confirm our hypothesis that the inter-eye relationship of microvasculature differs from that of the structural RNFL in POAG. Despite significant inter-eye asymmetry in RNFLT and VF loss, POAG subjects had similar cpVD asymmetry

as controls as demonstrated on two separate OCTA devices. Additional stratification based on specific subtypes of glaucoma yielded similar results: microvascular asymmetry did not significantly differ between controls and NTG or HTG subjects (Supplementary Table S3), nor between controls and subjects with increasing glaucoma severity (Supplementary Table S4). A subset of POAG subjects with macular imaging also demonstrated significantly increased GCC thickness asymmetry compared to controls but similar superficial VD asymmetry, further supporting our findings in the circumpapillary ONH (Table 3).

In the multivariable analyses, RNFLT asymmetry was significantly associated with MD difference between eyes (Table 4). In contrast, cpVD asymmetry was not significantly associated with either RNFLT or MD asymmetry (Table 5). Rather, only treated systemic hypertension was found to have significant association with reduced cpVD asymmetry (Table 5). Notably, alterations in systemic blood pressure directly relates to ocular blood flow, an important risk factor for vascular compromise of the optic nerve and development of glaucoma.[42–45] Changes in ocular perfusion pressure, a hemodynamic parameter defined as the difference between the mean arterial blood pressure and IOP, is hypothesized to generate ischemic insults to the ONH, resulting in glaucomatous damage.[46] Reduction of systemic blood pressure with antihypertensive treatment could potentially reduce ophthalmic perfusion pressure bilaterally and is associated with inter-eye microvascular symmetry. Additionally, impaired vascular autoregulation via neural and hormonal pathways are implicated in the pathophysiology of hypertension, which is widely thought to impact the perfusion state of peripheral organs including the eyes.[47–51] The association between treated hypertension and greater cpVD symmetry may reflect symmetric alterations in vascular autoregulation and remodeling in eyes with glaucomatous susceptibility. However, this study is unable to separate the effects of blood pressure treatment from the underlying hypertensive disease state due to its cross-sectional design.[51,52] Future studies might integrate real-time systemic hemodynamics such as ambulatory blood pressure monitoring or dynamic OCTA to better characterize this relationship.[53] We should note that we only assessed the association between treated hypertension and vessel density asymmetry between eyes, not the absolute degree of vessel density loss, as prior studies have indicated the potential negative effect of overtreated blood pressure on glaucoma progression.[54]

History of disc hemorrhage in the worse eye was also associated with increased cpVD asymmetry, although this association did not reach significance in the multivariable analysis. Disc hemorrhages have been associated with systemic autonomic dysregulation including low ocular perfusion pressure, low systolic blood pressure, and migraine headaches[45,55]; history of disc hemorrhage likely signifies additional microvascular vulnerability in the affected eye.[15,56] IOP asymmetry was also not shown to predict cpVD asymmetry. Although extreme fluctuations in IOP have been shown to impact ONH perfusion, all participants in this study had physiologic IOP on day of imaging, which has not been shown to impact OCT and OCTA parameters.[16,57–59]

Our findings have important implications to our understanding of microvascular compromise in POAG, as multiple lines of evidence suggest that vascular dysfunction in glaucoma has a systemic basis. POAG has been linked with systemic vasospastic conditions such as nocturnal hypotension, Raynaud's syndrome and migraines, implicating cardiovascular autonomic dysfunction in the pathogenesis of glaucoma.[43,60,61] Significant correlations of ophthalmic and nailfold microvasculature have been demonstrated in POAG subjects supporting a systemic etiology.[20,62,63] In our study, we demonstrated vascular dysfunction in POAG subjects by decreased circumpapillary vessel density in both eyes compared to control subjects and supported its systemic etiology by showing no significant inter-eye difference in vessel density compared to controls.

The inter-eye relationship of peripapillary microvasculature represents a multifactorial balance of ophthalmic and systemic determinants of optic disc blood flow. The specific association of OCTA asymmetry with a systemic hemodynamic parameter, rather than with structural and functional markers of glaucoma, suggests differences in vascular pathology and structural damage of POAG. In fact, a prior genome-wide association study has identified POAG risk loci with roles in vascular development, including *TEK, ANGPT1/2* and *SVEP1*, suggesting shared vascular susceptibility of both eyes for development of glaucoma.[64–67] Alternatively, the lack of significant cpVD asymmetry in POAG may be related to bilateral changes in microvasculature that precede disease manifestation in RNFL and visual function; in other words, vascular pathology in POAG may be an early and bilateral process. To this end, POAG subjects with unilateral visual field loss have been shown to have impaired ONH microcirculation in the contralateral unaffected eye.[68,69] Although our study was not designed to uncover a causative or temporal explanation given its cross-sectional design, our findings have important implications for understanding systemic versus ophthalmic determinants of ONH microvasculature and its difference from structural damage in POAG.

This study has some limitations. Our finding of lack of cpVD asymmetry in POAG could be impacted by measurement variability secondary to OCTA imaging methodology, although we applied strict imaging quality criteria for inclusion, achieved excellent inter-reader agreement on OCTA measurements (intraclass correlation coefficient = 0.953), and demonstrated similar findings on a second imaging device and in a different anatomic region of the eye (Table 3). Despite this, subtle impacts on OCTA measurements like media opacities, inaccurate segmentation, and inherent imaging variability between devices[70] cannot be excluded, although we showed consistent findings in two imaging devices and that signal quality did not affect OCTA asymmetry (Table 5). We also excluded subjects with high myopia to reduce potential segmentation artifacts from peripapillary atrophy and disc tilt on both OCT and OCTA measurements but could not exclude potential systemic bias in OCTA measurements because of RNFL thinning and optic nerve abnormalities in the POAG group.[71] Regardless, vessel density as measured by OCTA may not reflect actual blood flow of the optic nerve and can be susceptible to dynamic factors, including autonomic tone, heart rate, and systemic blood pressure.[16,72] Furthermore, this study lacked the resources to obtain same-day cardiac measurements including blood pressure and heart rate from all study participants, which would have further elucidated impact of systemic hemodynamics and autonomic tone on OCTA asymmetry.[16] Third, the impact of specific pressure-lowering drop medications on OCTA parameters was not controlled for in this study, although we had reliable records of same-day IOP measurements for most subjects. Fourth, this study was primarily conducted on White subjects which limits the generalizability of our findings to other racial groups. Last, this study is limited due to its cross-sectional design, and longitudinal studies would be required to draw conclusions regarding the role of vascular pathology on the susceptibility and onset of POAG. Although our methodology and findings provide a snapshot of the microvascular damage in POAG, future studies focused on dynamic assessments of the ONH microvasculature would elucidate the impact of vascular autoregulation in glaucoma.

Conclusions

POAG subjects demonstrated vascular compromise in both eyes yet similar cpVD asymmetry when compared to healthy controls despite significant differences in structural and functional loss between eyes in POAG subjects. Use of antihypertensive medications was associated with decreased microvascular asymmetry, highlighting the impact of systemic factors on ONH microvasculature. Meanwhile, ophthalmic factors related to glaucoma such as moderate-to-severe stage of disease, RNFLT asymmetry, and MD asymmetry were not associated with inter-eye vessel density asymmetry. This study highlights discordance between optic nerve structural change and microvascular compromise in POAG in a predominantly White population and emphasizes systemic determinants of glaucomatous pathology. Future studies with dynamic assessments of optic nerve vasculature, systemic blood pressure and in a more diverse study population may further clarify the relationship between the structural and microvascular abnormalities in glaucoma.

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