Vascular Density and Retinal Structure Relationships Across Sectors and Regions of the Optic Nerve in Patients With Primary Open Angle Glaucoma

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Précis: The relationship between structural and hemodynamic parameters in patients with primary open angle glaucoma is strongest in the temporal region of the optic nerve.

Purpose: To investigate the relationship between radial peripapillary capillary (RPC) vessel density (VD) and retinal nerve fiber layer (RNFL) thickness in quadrants and sectors of the optic nerve head (ONH) in patients with and without primary open angle glaucoma (POAG).

Methods: In a cross-sectional prospective analysis, 191 subjects (80 early-stage POAG; 111 non-glaucomatous controls) were assessed for RNFL thickness and RPC VD in each quadrant [superior (S), inferior (I), nasal (N) and temporal (T)] and sector [inferior-temporal (IT), temporo-inferior (TI), temporo-superior (TS), superior-temporal (ST), inferior-nasal (IN), naso-inferior (NI), naso-superior (NS), and superior-nasal (SN) sectors] of the ONH through optical coherence tomography angiography (OCTA). Pearson correlations were used to test for associations between measurements, with $P < 0.05$ considered statistically significant.

Results: Significantly stronger positive correlations were found between RPC VD and RNFL thickness in the S, I, and T quadrants in POAG patients compared with non-glaucomatous controls (all $P < 0.05$). The temporal quadrant in POAG patients displayed the largest difference in correlation compared with controls. A stronger positive correlation was also found between RPC VD and RNFL thickness in the temporal sectors of the ONH in POAG patients compared with controls, with the largest difference in the TS sector (all $P < 0.05$).

Conclusion: Early-stage POAG patients have a stronger relationship between RPC VD and RNFL in the temporal regions of the ONH compared with non-glaucomatous controls, with the TS sector demonstrating the largest difference between groups. Temporal sector VD loss may represent an early-stage biomarker for vascular-linked POAG disease.

Key Words: primary open angle glaucoma, optical coherence tomography angiography, optic nerve head, retinal nerve fiber layer, radial peripapillary capillary vessel density

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Prior studies have demonstrated that individuals with primary open angle glaucoma (POAG) exhibit altered retinal and optic nerve head (ONH) structure when compared with healthy controls.[1] Specifically, individuals with POAG have a thinner retinal nerve fiber layer (RNFL) than non-glaucomatous persons, which is a hallmark of the disease.[2,3] Although risk stratification has historically been based largely on elevated intraocular pressure (IOP), many persons develop and continue to progress in POAG disease despite medically lowered pressures.[4] Other contributing factors to glaucomatous disease include advancing age, myopia, being of African descent, and disruption of ocular hemodynamics and oxygen metabolism.[1,5–7] The specific factor(s) that drive different patterns of RNFL or functional loss observed in POAG are currently unknown.

Significant research demonstrates POAG patents have reduced retinal and ONH circulations compared with persons without glaucoma, although the specific impact of lower perfusion biomarkers on disease metrics remains largely elusive.[5–7] POAG diagnostics are complicated by the high variation in the signs and appearance of glaucoma. For

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instance, in the ocular hypertensive treatment study (OHTS) the first detectable changes were in structure, while in the Early Manifest Glaucoma Trial (EMGT) visual field changes most frequently appeared first.[8] A recent longitudinal study in POAG patients found that despite lower IOP over a 5-year period, lower retinal capillary blood flow in the superior retina was significantly associated with structural disease progression.[9] In addition, POAG patients of African descent have been shown to have a stronger vascular component to their structural disease progression compared with those of European descent.[10] These observations, along with variations in patient populations and disease status, reflect that vascular-driven changes may affect RNFL and functional loss in POAG differently compared with IOP-driven glaucomatous damage.

Advancements in optical coherence tomography (OCT) and OCT angiography (OCTA) allow for a high specificity of detail in describing both structural and hemodynamic components within various anatomic subregions of the retina.[10–17] Previous research using OCTA has identified lower vascular densities (VD) in the retina and tissues surrounding the ONH in patients with POAG that correlate with reduced visual function.[12,13,18–23] Conversely, a recent study in early glaucoma patients found that OCT and OCTA biomarkers had only fair agreement with functional outcomes, yet they were able to detect glaucomatous changes more sensitively and timely than visual field testing.[14] In certain patients, various OCTA VD biomarkers have been shown to be equal to or more sensitive than RNFL when diagnosing POAG.[18–20,22] In contrast, a study of early-stage POAG patients found significantly weaker prognostic ability of temporal and inferotemporal peripapillary VD compared with RNFL.[21] These diverse diagnostic data suggest POAG may represent a collection of disease traits and progression patterns brought upon by elevated IOP, reduced ONH circulation, and/or a combination of both physiological sequences.

The order of events ultimately leading to retinal ganglion cell (RGC) loss in POAG are largely unknown, as is the expected first signs and observable appearance of the disease. Although highly variable, POAG often affects specific retinal regions before the disease displaying global deficits as demonstrated by Garway-Heath Maps of visual function.[15] The first location of RNFL loss in POAG is also highly individual, occurring in different sectors of the ONH linked to specific 24-2 visual field locations.[24] OCTA-assessed VD and RNFL thickness may display similar relationships within sectors and regions of the ONH, and the studies suggested that VD in the inferior and superior sectors of the superficial capillary plexus in the peripapillary region are the most discriminative in diagnosing POAG.[16]

Informing on the relationship of VD and RNFL thickness in specific sectors of the ONH in early-stage POAG may provide insight into the initial sequences of reduced vascularity, tissue regression, and visual function. This study, therefore, investigates differences in relationships between RNFL thickness and OCTA-assessed VD biomarkers calculated by global score, hemisphere, quadrant, and individual sector of the ONH in early-stage POAG patients and non-glaucomatous controls.

MATERIAL AND METHODS

In a prospective cross-sectional analysis, 191 individuals (80 early-stage POAG patients and 111 non-glaucomatous controls) were enrolled at the Icahn School of Medicine at Mount Sinai, New York, NY. All individuals received, reviewed, and signed a written informed consent before engaging in this study. This study was performed in compliance with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of Icahn School of Medicine at Mount Sinai, New York, NY (study-20-00198; approval date: April 19, 2020). Enrolled participants were required to be at least 21 years of age and understand the informed consent.

All the eye measurements were performed only in the study eye and a coin flip was utilized to include randomly selected qualified eyes for each study participant. A certified glaucoma specialist determined POAG status considering the presence of an open angle and structural and functional exam findings consistent with glaucomatous damage. Early stage POAG was defined based on the Hodapp-Parrish-Anderson classification (mean deviation (MD): ≥ -6 dB).[25] The non-glaucomatous control eyes consisted of participants with both eyes being free of any eye diseases including POAG. Inclusion criteria for all participants included age 21 years or older and no other eye diseases. Exclusion criteria included: refractive error $> +9$ Diopters and < -9 Diopters in spherical equivalent; severe glaucoma (legally blind or near blind); evidence of exfoliation or pigment dispersion; eye disease other than glaucoma; use of ocular medications (other than IOP lowering medications for glaucoma or eye lubricants for dry eye); neurological disease; psychosis or other diseases that could prevent reliable eye exams; and severe, unstable, or uncontrolled cardiovascular, renal, or pulmonary disease.

Study participants recruited during a scheduled appointment with an ophthalmologist or self-referred underwent a single 2-hour study visit. Demographics, including age, self-reported race and ethnicity, biological sex, height, weight, diabetic status, hypertensive status, and ocular and systemic medication use were recorded. Participants underwent assessment for: visual field parameters MD, pattern standard deviation (PSD), and visual field index (VFI) through 24-2 Sita Standard, Zeiss Humphrey Visual Field Analyzer (Carl Zeiss Meditec Inc., Dublin, CA), IOP through Goldmann applanation, heart rate (HR) and blood pressure (BP) [systolic (SBP) and diastolic (DBP)] through automated ambulatory BP monitor after 5 minute rest. Mean arterial pressure (MAP) and ocular perfusion pressures (OPP) were calculated using the equations $MAP = [SBP + (2 \times DBP)]/3$ and $OPP = 2/3 \times MAP\text{-}IOP$.

OCTA imaging was assessed through the RTVue XR Avanti System (RTVueXR, Version 2018.1.1.63; Optovue Inc., Fremont, CA). This imaging modality provided a noninvasive 3-dimensional visualization of the retinal microvasculature and OCT-derived structural parameters at the level of the ONH. AngioAnalytics TM licensed upgrade was utilized to provide VD analysis computed as a percentage of area occupied by OCTA detected vasculature at the level of the ONH.[26] VD was assessed for the small vessels [ie, with large vessel masking; the large vessel mask had a threshold of ≥ 3 pixels ($\sim \geq 33$ μm)]. The 4.5 mm HD Angio Disc scan was used to assess small vessels VD in the radial peripapillary capillary (RPC) slab ranging from the internal limiting membrane to the nerve fiber layer in the peripapillary region (delineated by 2 rings of 2 and 4 mm centered on disc center), at a global, hemispheric [superior (S) and inferior (I), quadrant (S, I, temporal (T), nasal (N))], and sectorial [inferior-temporal (IT), temporo-inferior (TI), temporo-superior (TS), superior-temporal (ST), inferior-nasal (IN), naso-inferior (NI), naso-superior (NS), and superior-nasal (SN)]

level. Peripapillary RNFL thickness was also measured at a global, hemispheric (S and I), quadrant (S, I, T, N), and sectorial (IT, TI, TS, ST, IN, NI, NS, and SN) level. Images were only analyzed if they had a scan quality indicator of 6 and above. Further information regarding OCTA may be found here.[11,13,17,26]

POAG patients and controls were compared for differences in patient characteristics (age, BMI, and sex) using 2-sample t tests and χ^2 tests. ANOVA was used to compare differences in BP, HR, IOP, and visual field MD, PSD, and VFI%, adjusted for sex, race, and age. Repeated measures ANOVA was used to compare quadrants and among sectors within and between POAG and non-glaucomatous controls. Pearson correlations were used to test for associations between measurements, with the Fisher Z tests used to compare between POAG patients and controls for differences in correlations. A 2-sided 5% significance level was used for all tests. Analyses were performed using R statistical software, version 4.2.3 (https://cran.r-project.org/).

RESULTS

Study participant demographics and ocular and systemic parameters are presented in Table 1. Before statistical age-adjustment, POAG patients were significantly older than non-glaucomatous controls. VF MD was significantly lower, and PSD was significantly higher in POAG patients compared with controls. No significant differences were observed between POAG and non-glaucomatous controls for BPs, OPP, HR, IOP, or VFI (all $P > 0.05$).

Table 2 depicts the RNFL thickness in both POAG patients and non-glaucomatous controls. RNFL thickness measurements in patients with POAG were significantly lower than controls at the global, hemispheric, quadrants, and sectorial levels (all $P < 0.0001$), Figure 1.

RPC VD was significantly lower in POAG patients than non-glaucomatous controls for all of the 8 individual sectors ($P = 0.0005$ for TS, $P = 0.0003$ for TI, and $P < 0.0001$ for all other sectors). The differences between POAG and controls were largest for IN and IT sectors, followed by SN and ST, then NI and NS. In addition to the mean differences between POAG and controls, the variability of the VD measurements in each sector were significantly higher ($P < 0.001$) for glaucoma than in non-glaucomatous controls. Focusing on the subjects with POAG, VD were highest in TS ($P < 0.01$ compared with all other sectors), with densities in IT, TI, and ST also significantly greater than VDs in NS, IN, SN, and NI sectors ($P < 0.001$). Figure 2 shows the box plots of OCTA VD in the 8 sectors for POAG and control. Measurements indicate a variation in VD by spatial region, both between and within glaucoma status groups. Table 3 depicts the RPC VD measured by OCTA in POAG and non-glaucomatous controls.

In the examination of relationships between variables, significantly higher (positive) correlations were found between RNFL thickness and RPC VD in the S, I, and T quadrants of POAG patients compared with non-glaucomatous controls (all $P < 0.05$). The temporal quadrant in individuals with POAG displayed the largest difference in correlation compared with controls (Fig. 3). A stronger positive correlation was also found between RPC VD and

TABLE 1. Mean and SD of Demographic, Ocular, and Systemic Parameters in Primary Open Angle Glaucoma (POAG) Patients and Healthy Controls

	Study participants	Mean (SD)	P control vs. POAG
Age at visit (y)	Control	42.69 (16.91)	< 0.0001*
	OAG	66.61 (12.54)	
Sex ratio (male:female)	Control	38%:62%	0.1818
	OAG	48%:52%	
Race ratio (European descent: non-European descent)	Control	39%:61%	0.0260*
	OAG	55%:45%	
BMI	Control	27.11 (6.96)	0.0419*
	OAG	25.03 (6.81)	
IOP (mm Hg)	Control	14.64 (2.99)	0.7217
	OAG	15.93 (5.41)	
SBP (mm Hg)	Control	121.20 (15.92)	0.7684
	OAG	128.84 (17.47)	
DBP (mm Hg)	Control	76.50 (10.35)	0.8515
	OAG	78.03 (11.26)	
MAP (mm Hg)	Control	91.4 (11.38)	0.8171
	OAG	95.00 (12.28)	
OPP (mm Hg)	Control	46.36 (8.13)	0.6939
	OAG	47.49 (9.53)	
Heart rate (bpm)	Control	73.27 (12.28)	0.6109
	OAG	70.48 (15.41)	
Visual field MD (decibel)	Control	−1.19 (2.13)	0.0073*
	OAG	−2.24 (3.12)	
Visual field PSD (decibel)	Control	2.28 (2.03)	0.0177*
	OAG	3.45 (2.40)	
Visual field VFI (%)	Control	95.83 (13.78)	0.2330
	OAG	93.26 (12.65)	

*$P < 0.05$.

BMI indicates body mass index; bpm, beats per minute; DBP, diastolic blood pressure; IOP, intraocular pressure; MAP, mean arterial pressure; MD, mean deviation; OPP, ocular perfusion pressure; PSD, pattern standard deviation; SBP, systolic blood pressure; VFI, visual field index.

TABLE 2. Mean and SD Measurements for Retinal Nerve Fiber Layer (RNFL) Thickness and Comparisons (*P*-Values) for Primary Open Angle Glaucoma (POAG) Patients and Healthy Controls

RNFL thickness	Subjects	Mean (SD)	*P* control vs. POAG
Global	Control	111.71 (13.92)	<0.0001*
	OAG	85.10 (13.46)	
Superior hemisphere	Control	111.95 (14.17)	<0.0001*
	OAG	85.90 (14.28)	
Inferior hemisphere	Control	111.44 (15.46)	<0.0001*
	OAG	83.92 (16.04)	
Superior quadrant	Control	133.16 (19.05)	<0.0001*
	OAG	96.20 (19.02)	
Inferior quadrant	Control	143.06 (21.47)	<0.0001*
	OAG	101.71 (24.17)	
Temporal quadrant	Control	73.23 (11.79)	<0.0001*
	OAG	64.67 (13.03)	
Nasal quadrant	Control	99.88 (18.53)	<0.0001*
	OAG	78.29 (14.47)	
IN sector	Control	144.72 (31.31)	<0.0001*
	OAG	100.63 (26.43)	
IT sector	Control	141.22 (22.75)	<0.0001*
	OAG	103.65 (29.45)	
NI sector	Control	89.02 (20.59)	<0.0001*
	OAG	71.11 (14.70)	
NS sector	Control	108.72 (19.66)	<0.0001*
	OAG	84.00 (16.74)	
SN sector	Control	136.96 (25.90)	<0.0001*
	OAG	95.15 (20.07)	
ST sector	Control	128.59 (22.05)	<0.0001*
	OAG	96.91 (25.81)	
TI sector	Control	70.10 (13.28)	<0.0001*
	OAG	61.31 (14.64)	
TS sector	Control	76.03 (12.58)	<0.0001*
	OAG	67.30 (13.99)	

*$P < 0.05$.

IN indicates inferior-nasal; IT, inferior-temporal; NI, naso-inferior; NS, naso-superior; SN, superior-nasal; ST, superior-temporal; TI, temporo-inferior; TS, temporo-superior.

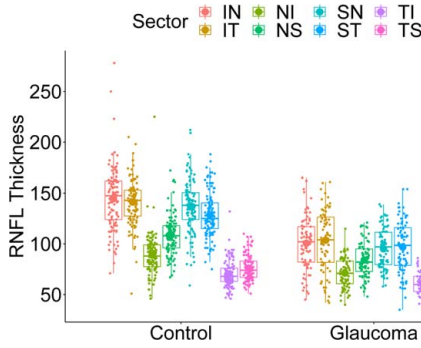

FIGURE 1. Box plots of measured retinal nerve fiber layer (RNFL) thickness for each patient in each of the 8 sectors, separated by non-glaucomatous controls (left) and primary open angle glaucoma patients (right). The different colors indicate vessel densities in the inferior-nasal (IN), inferior-temporal (IT), nasal-inferior (NI), nasal-superior (NS), superior-nasal (SN), superior-temporal (ST), temporal-inferior (TI), and temporal-superior (TS) sectors. Figure 1 can be viewed in color online at www.glaucomajournal.com.

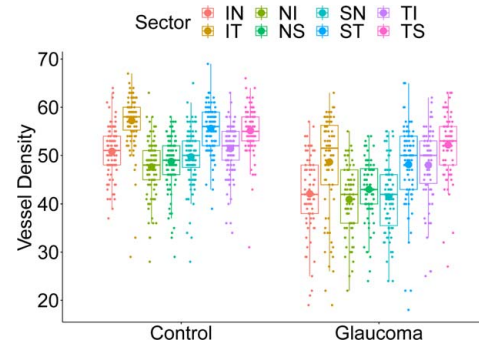

FIGURE 2. Box plots of measured vessel densities for each patient in each of the 8 sectors, separated by non-glaucomatous controls (left) and primary open angle glaucoma patients (right). The different colors indicate vessel densities in the inferior-nasal (IN), inferior-temporal (IT), nasal-inferior (NI), nasal-superior (NS), superior-nasal (SN), superior-temporal (ST), temporal-inferior (TI), and temporal-superior (TS) sectors. Figure 2 can be viewed in color online at www.glaucomajournal.com.

RNFL thickness in the temporal sectors (IT, TI, TS, and ST) in POAG patients compared with controls (all $P < 0.05$). The TS sector of the ONH showed the largest

TABLE 3. Mean and SD Measurements for Vessel Densities and Comparisons (*P*-Values) for Primary Open Angle Glaucoma (POAG) Patients and Healthy Controls

Vessel density (%)	Subjects	Mean (SD)	*P* control vs. POAG
Global	Control	48.99 (3.01)	<0.0001*
	OAG	43.38 (4.42)	
Superior hemisphere	Control	51.92 (3.70)	<0.0001*
	OAG	46.01 (5.77)	
Inferior hemisphere	Control	51.43 (3.97)	<0.0001*
	OAG	44.56 (6.35)	
Superior quadrant	Control	52.47 (4.60)	<0.0001*
	OAG	44.56 (7.05)	
Inferior quadrant	Control	53.74 (4.67)	<0.0001*
	OAG	44.96 (7.84)	
Temporal quadrant	Control	53.43 (4.28)	0.0002*
	OAG	50.35 (6.54)	
Nasal quadrant	Control	48.25 (5.07)	<0.0001*
	OAG	42.08 (6.36)	
IN sector	Control	50.84 (5.05)	<0.0001*
	OAG	42.12 (8.03)	
IT sector	Control	57.23 (5.30)	<0.0001*
	OAG	48.63 (10.20)	
NI sector	Control	47.61 (5.59)	<0.0001*
	OAG	40.94 (7.28)	
NS sector	Control	48.73 (5.28)	<0.0001*
	OAG	43.01 (6.34)	
SN sector	Control	49.69 (5.57)	<0.0001*
	OAG	41.48 (7.52)	
ST sector	Control	55.60 (4.63)	<0.0001*
	OAG	48.10 (8.57)	
TI sector	Control	51.43 (5.07)	0.0003*
	OAG	48.00 (7.55)	
TS sector	Control	55.15 (4.59)	0.0005*
	OAG	52.18 (6.78)	

*$P < 0.05$.

IN indicates inferior-nasal; IT, inferior-temporal; NI, naso-inferior; NS, naso-superior; SN, superior-nasal; ST, superior-temporal; TI, temporo-inferior; TS, temporo-superior.

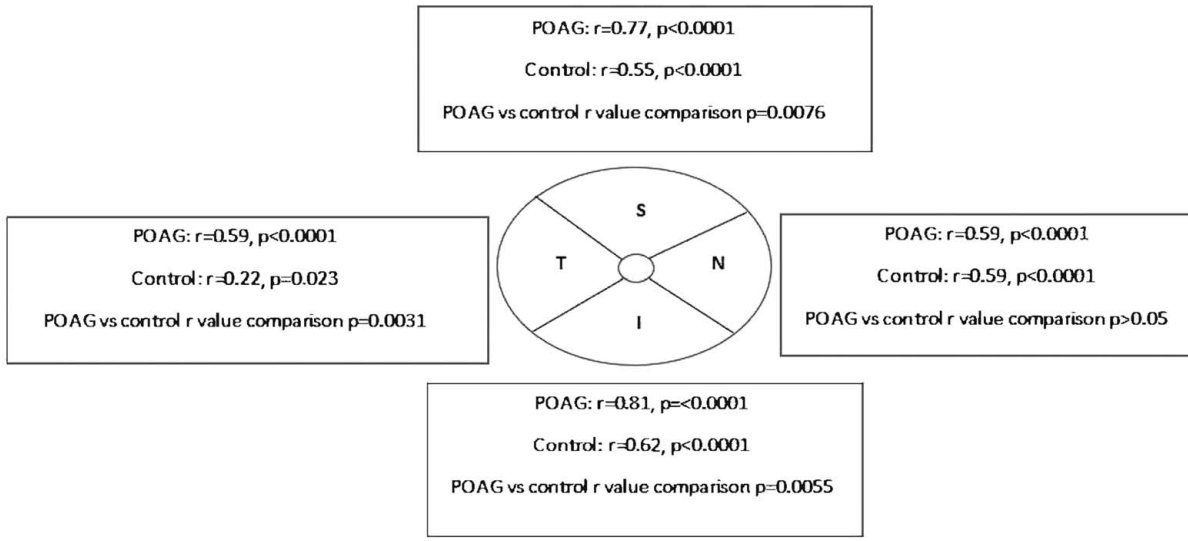

FIGURE 3. Pearson correlations (*r*) used to test for associations between retinal nerve fiber layer thickness and vessel densities at the quadrant level by primary open angle glaucoma (POAG) status, with Fisher *Z* tests used to compare between POAG patients and non-glaucomatous controls for differences in correlations. I indicates inferior quadrant; N, nasal quadrant; S, superior quadrant; T, temporal quadrant.

difference between POAG patients and non-glaucomatous controls (Fig. 4).

DISCUSSION

The enigma of glaucoma and blood flow may be best understood at the earliest stages of the disease before significant RGC death, tissue regression, and vision loss. It is likely that in many patients, elevated IOP is the major cause of disease, while in others loss of capillaries surrounding the ONH may initiate cellular damage. The signs and symptoms of POAG, including RNFL loss, appear heterogeneously among patients, and little is known about the differential drivers of structural versus functional disease progression patterns. While hemodynamic disturbances have long been associated with POAG disease, data on sectorial vascular changes occurring before visual field loss are largely missing. Incorporating sector-specific OCTA VD assessments early, before significant disease, may help inform and significantly improve glaucoma diagnostics.[18–24]

Previous studies investigating IOP-independent mechanisms of POAG insult have linked thinner RNFLs and reduced retinal VD at global levels.[6,13] Our results agree with these previous studies indicating that individuals with

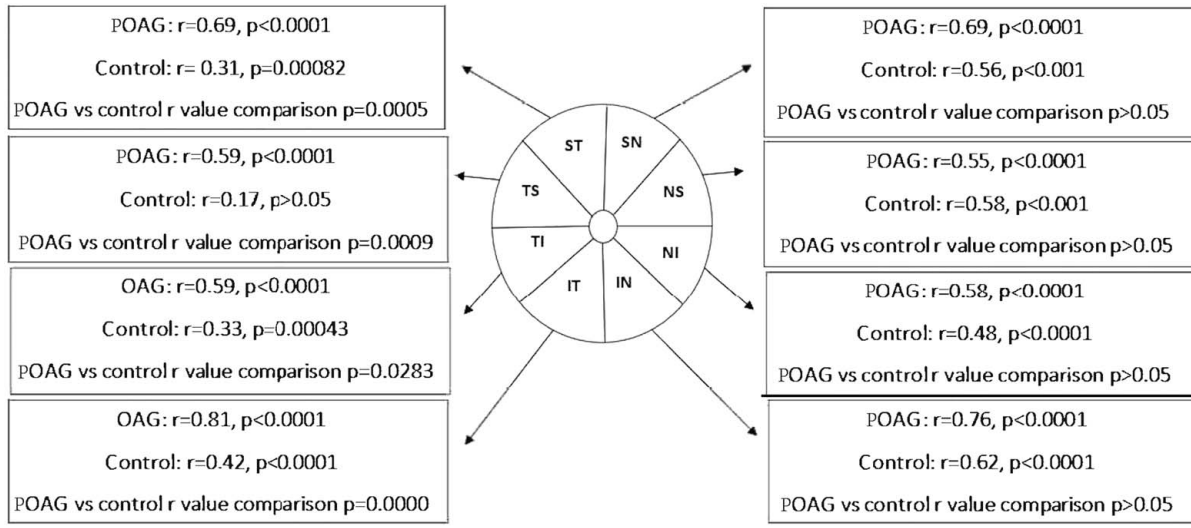

FIGURE 4. Pearson correlations (*r*) used to test for associations between retinal nerve fiber layer thickness and vessel densities at the sectorial level by primary open angle glaucoma (POAG) status, with Fisher *Z* tests used to compare between POAG patients and non-glaucomatous controls for differences in correlations. IN indicates inferior-nasal sector; IT, inferior-temporal sector; NI, nasal-inferior sector; NS, nasal-superior sector; SN, superior-nasal sector; ST, superior-temporal sector; TI, temporal-inferior sector; TS, temporal-superior sector.

POAG have a thinner RNFL and reduced VD when compared with non-glaucomatous controls. These significant differences were true at both global and regional levels (Tables 1,2). Peripapillary RNFL thickness measurements were significantly lower in patients with POAG at the global, hemispheric, quadrant, and sectorial level (all $P < 0.0001$). OCTA-assessed VD were also significantly lower for POAG patients than controls for all the individual sectors ($P = 0.0005$ for TS, $P = 0.0003$ for TI, and $P < 0.0001$ for all other sectors). In contrast, the relationships between RNFL thickness and RPC VD were not significantly ($P > 0.05$) different at the whole image or hemisphere levels between POAG patients and non-glaucomatous controls. In the clinical practice, ophthalmologists often evaluate only average/global RNFL thickness as the main biomarker of disease. However, sectorial damage may be masked by average and global RNFL thickness within normal limits, and individuals with structural damage localized only at a sectorial level may go undetected and their treatment may ultimately be delayed. Our results suggest the importance to assess both structural and hemodynamic parameters both at a global and regional level, as statistical significance between individuals with POAG and non-glaucomatous controls was only reached when assessing these structural-hemodynamic relationships at the quadrant and sector levels. It is important to note that our patients were early-stage POAG and these results may not apply to more severe stages of POAG. Overall, these data indicate that using only global assessments of mean RNFL thickness and VD may mask significant vascular-linked structural damage in early-stage POAG patients.

Historical efforts to use ocular blood flow biomarkers to compliment RNFL assessments for glaucoma diagnostics have included data from retrobulbar blood vessels.[27] With improvements in scanning and specificity, OCTA-assessed VD exams have demonstrated high discriminatory abilities for diagnosing POAG that are in line with or superior to the measurement of RNFL.[13,18–22] In an interesting study Bayraktar et al[28] compared the RPC VD and RNFL thickness in adults with a maternal or paternal history of POAG with age-matched healthy subjects without a family history of disease. While RNFL thickness was not significantly different between the 2 groups, subjects with a positive family history of POAG presented significantly lower whole image and average RPC VD than the age-matched controls (whole image: $51.6\% \pm 1.7\%$ vs. $49.8\% \pm 1.7\%$, $P = 0.0006$; average: $54.7\% \pm 1.7\%$ vs. $53.2\% \pm 2.1\%$, $P = 0.006$).[28] This study suggests the potential role of RPC VD as an early biomarker of disease, even before structural changes occur. However, not all studies agree, as a study of 39 POAG and 53 control subjects found the diagnostic ability of the OCTA VD to be only moderate.[23] Researchers specifically found peripapillary VD to have significantly higher diagnostic abilities than macular and inside disc regions.[23]

In our analysis, significantly stronger positive relationships were also found between RNFL thickness and RPC VD in the S, I, and T quadrants of POAG patients compared with non-glaucomatous controls (all $P < 0.05$). Compared with non-glaucomatous controls, POAG patients displayed the largest difference in correlation in the temporal quadrant of the ONH as seen in Figure 3. In addition, a stronger positive correlation was also found between RPC VD and RNFL thickness in the temporal sectors (IT, TI, TS, and ST) of the ONH in POAG patients with the TS sector showing the largest difference ($P = 0.0009$) between POAG patients and controls (Fig. 4). This is an interesting finding as results from previous studies have shown that glaucomatous damage often occurs in the inferotemporal region of the ONH. The superotemporal region, however, has also been found to be the second region most frequently affected by RNFL defects (RNFLD).[29,30] Specifically, Leung et al[29] assessed the RNFL thickness with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA) in 116 glaucoma patients and 113 non-glaucomatous controls and found that the inferotemporal meridians, followed by the superotemporal ones, were the most frequently affected by RNFLD. Mansoori et al,[31] using the OCTA RTVue XR-100 (Avanti OCT), found that in early POAG patients capillary density was significantly lower in both the inferotemporal and superotemporal sectors compared with non-glaucomatous controls, with corresponding RNFLD. The use of different OCT(A) devices (with different specific topographical criteria to define sectorial regions), together with specific characteristics of study populations, may have also significantly impacted results and limit comparability. A previous study of 113 healthy eyes and 140 glaucomatous eyes found the area under the receiver operating characteristic curves (AUCs) to be higher for the average peripapillary VD than the ONH and macular region (AUCs: 0.807, 0.566, and 0.651, respectively) for glaucoma detection.[21] Importantly, in the early stage of glaucoma, the AUCs of the inferotemporal and temporal peripapillary VD were significantly lower than that of the RNFL thickness.[21] Another study of 39 POAG patients and 53 control subjects found the AUC of the average peripapillary VD to be significantly better than the average inside disc and macular VD, while the VD AUC of all regions were negatively associated with the visual field MD.[23] Furthermore, 1 study of 63 POAG eyes and 48 healthy control eyes assessed the diagnostic capabilities of OCTA-derived peripapillary VD and OCT-derived RNFL thickness, finding that AUC was highest for VD in the inferotemporal sector while the highest AUC for RNFL thickness was in the inferonasal sector (AUC at 0.88 and 0.91, respectively).[32] These results indicate that OCTA-derived peripapillary VD have comparable diagnostic ability to RNFL thickness. Together these data suggest RNFL and VD loss are both linked to POAG but with specific sectors demonstrating first glaucoma defect or best AUC depending on the study.

Our study has some limitations to consider, including a cross-sectional study design. Given the inability of this study to capture relationships over time, future studies are needed to assess the predictive value of RPC VD for disease progression. Diurnal variability of VD measurements were not assessed in this study, however, previous studies have suggested that OCTA-derived VD measurements do not change significantly based on the time of day.[33] Another limitation of our study is represented by the fact that the non-glaucomatous control group was significantly younger than the POAG group. Since age has been shown to impact both OCTA-derived VD and RNFL thickness,[34,35] our results were statistically adjusted for age to help account for this limitation. In addition, our results were also statically adjusted for race, as study groups varied in their racial compositions, with the overall POAG group including more white participants than the overall control group. Another important feature to consider but not assessed in the current investigation is axial length. Axial length has been shown to be negatively correlated to both RNFL thickness and superficial peripapillary VD.[36] In our study, axial length has

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not been measured, although refractive errors > +9 diopters or < −9 diopters were excluded. It is important to also highlight that both systemic and topical medications have been shown to affect OCTA-derived vascular measurements.[37–39] For example, systemic medications such as sildenafil have been shown to increase outer retinal blood flow densities, while topical antiglaucoma drops increase both flow and VD in peripapillary regions.[37–39] However, in our study, the influence of topical and systemic medications were not investigated. In addition to the mean differences between POAG and controls, we found the variability of the VD measurements in each sector were significantly higher ($P < 0.001$) for POAG than non-glaucomatous controls. Higher variability of VD in POAG patients in our relatively small sample size may limit detectability and significance. In this analysis, we focused on RNFL measures captured at the peripapillary level surrounding the ONH, potentially missing important hemodynamic insights inside the optic disc. Nevertheless, our study has the benefit of using OCTA for quantifying RNFL thickness and VD biomarkers across sectors and regions of the ONH in a single session by a single operator (A.V.V.) thereby limiting spatial and operator errors between measures and subjects.

Although our data and previous study results[18–23] contain nonuniform populations and differing approaches, a consensus of the data suggests OCTA-assessed VD in specific sectors and regions of the ONH appear to be differentially affected by POAG, with each having differing diagnostic abilities. As demonstrated by the major findings of the OHTS and EMGT, POAG damage is highly variable and may first be detected structurally or functionally, often depending on the patient population, diagnostic methodologies, and a patient's glaucoma status. Persons of African descent have significantly higher rates of cardiovascular disease,[40] which may be potentially contributing to retinal capillary loss and their outsized rates of glaucomatous disease.[10] Our findings, therefore, suggest significant reductions in VD between POAG patients across all sectors and regions of the ONH and highlight that the relationship between VD and RNFL is sector specific. Our data also suggest that only evaluating global averages may mask hidden segments of capillary loss within specific segments of ONH tissues. The temporal regions of the ONH may be most sensitive to VD loss in early POAG, although temporal RNFL and VD diagnostic abilities may be lower overall for determining POAG status. Future research should consider sectorial analysis for RNFL and VD based upon both reports of higher AUC by segment and the potential to reveal unobserved areas of nonperfusion when OCTA VD biomarkers are subdivided in patients with POAG.

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