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Retinal Blood Flow in Glaucomatous Eyes with Single Hemifield Damage

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Abstract

Purpose—To examine the hypotheses that in glaucomatous eyes with single-hemifield damage, retinal blood flow (RBF) is significantly reduced in retinal hemisphere corresponding abnormal visual hemifield; and that there are significant associations between reduced retinal sensitivity (RS) in abnormal hemifield, RBF, and structural measurements in the corresponding hemisphere.

Design—prospective, non-randomized, case-control study.

Participants—Thirty eyes of 30 glaucoma patients with visual field loss confined to a single hemifield, and 27 eyes of 27 controls.

Methods—Normal and glaucomatous eyes underwent Spectral-domain optical coherence tomography (SDOCT) and standard automated perimetry. Doppler SDOCT with a double-circle scanning pattern was used to measure RBF. RBF was derived from the recorded Doppler frequency shift and the measured angle between the beam and the vessel. Total and hemispheric RBF, retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) values were calculated. The retinal sensitivity values were converted to 1/Lambert. Analysis of variance and regression analyses were performed.

Main outcome measures—Total and hemispheric retinal sensitivity, RBF, RNFL and GCC values.

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Results—The total RBF (34.6±12.2μL/min) and venous cross sectional area (0.039±0.009mm^2) were reduced (p<0.001) in glaucoma compared with controls (46.5±10.6; 0.052±0.012mm^2). Mean RBF was reduced in abnormal hemisphere compared to the opposite hemisphere (15.3±5.4 vs 19.3±8.4μL/min, p=0.004). The RNFL and GCC were thinner in the corresponding abnormal hemisphere compared with the opposite hemisphere (87.0±20.2, 103.7±20.6μm, p=0.002; 77.6±12.1 and 83.6±10.1μm, p=0.04). The RBF was correlated with RNFL (r=0.41, p=0.02) and GCC (r=0.43, p=0.02), but not the retinal sensitivity (r=0.31, p=0.09) in the abnormal hemisphere. The RBF (19.3±8.4μL/min), RNFL (103.7±20.6μm) and GCC (83.6±10.1μm) were reduced (p<0.05) in the hemisphere with apparently normal visual field in glaucomatous eyes compared with the mean hemispheric values of the normal eyes (23.2±5.3μL/min; 124.8±9.6μm; 96.1±5.7μm respectively).

Conclusions—In glaucomatous eyes with single-hemifield damage, the RBF is significantly reduced in the hemisphere associated with the abnormal hemifield. Reduced RBF is associated with thinner RNFL and GCC in the corresponding abnormal hemisphere. Reduced RBF, and RNFL and GCC loss are also observed in the perimetrically-normal hemisphere of glaucomatous eyes.

Keywords

retinal blood flow; glaucoma; hemifield damage; visual field; Doppler spectral-domain optical coherence tomography

Introduction

Background and Hypothesis

Glaucoma is a multifactorial optic neuropathy and vascular factors have been suggested to be significant contributors to the development and progression of glaucomatous optic neuropathy and visual field loss.[1–5] Different studies have demonstrated that in primary open angle glaucoma (POAG) the blood flow is diminished in the optic nerve head (ONH), retina and choroid.[4,8–10] The retinal ganglion cells (RGCs), retinal nerve fiber layer (RNFL) and their axons in the inner retina are supplied by the retinal circulation, through the central retinal artery (CRA) via the ophthalmic artery.[9] Several studies have shown associations between the attenuation of retinal vessels and the severity of glaucomatous damage.[11–13]

Doppler Spectral-domain optical coherence tomography (SDOCT) is a reliable and repeatable technique[4,15,16] that measures the Doppler shift of reflected light due to moving blood cells and allows calculation of the total and hemispheric vein velocity and area. To compute the flow in the vessel, the technique requires measurement of the angle of the vessel relative to the scanning beam, which can be obtained using a dual circumpapillary scanning strategy. Several studies have demonstrated decreased retinal blood flow (RBF) in glaucomatous eyes compared with normal eyes using this technique.[15–17]

Many studies have demonstrated that eyes with visual field loss confined to a single visual hemifield have diffuse RNFL atrophy suggesting that relatively widespread structural injury may precede localized functional loss as measured using standard automated perimetry (SAP).[18–20] Longitudinal data to support this hypothesis, or the mechanism by which it occurs, is limited. We hypothesized that eyes with single-hemifield glaucomatous damage may have significantly reduced RBF in the hemifield corresponding with the visual field loss compared with the normal hemifield, and that normal hemifield has reduced RBF relative to normal controls. This study was conducted to examine the relationship between RBF, retinal sensitivity and parapapillary and macular structural measurements in glaucomatous eyes with single-hemifield damage compared with the normal eyes.

Methods

Study Population

The subjects were participants of the Advanced Imaging for Glaucoma (AIG) study, a prospective, non-randomized, multi-center, longitudinal clinical trial of normal, glaucoma suspect, pre-perimetric glaucoma, and perimetric open angle glaucoma patients (www.AIGStudy.net. Accessed September 12, 2013).

Patients consisted of perimetric glaucoma patients with ≥ 28 months of follow-up who were enrolled at Bascom Palmer Eye Institute, University of Miami; Doheny Eye Institute, University of Southern California, and the Casey Eye Institute, Oregon Health and Science University. Informed consent was obtained from all subjects using the consent forms approved by the Institutional Review Boards (IRB) of the participating institutions, which were in agreement with the provisions of Declaration of Helsinki. The study was in accordance with The Health Insurance Portability and Accountability Act of 1996 (HIPPA) privacy and security regulations.

Inclusion criteria common to both normal and glaucoma groups consisted of reliable SAP defined as < 15% rate of fixation loss and < 33% rates of false positive and false negative errors, spherical equivalent refractive error between −7.00 and +3.00 diopters sphere, best-corrected visual acuity (BCVA) of 20/40 or better, age ≥ 40 and ≤ 80 years, and no prior history of intraocular surgery except for uncomplicated cataract extraction. Standard automated perimetry was performed in normal and glaucoma subjects using Swedish Interactive Threshold Algorithm (SITA) standard 24-2 threshold test (Humphrey Field Analyzer 750 II-I, Carl Zeiss Meditec, Inc., Dublin, CA, USA).

Inclusion criteria for the normal group were defined as IOP ≤ 21mmHg, normal appearing ONH, intact neuroretinal rim and RNFL, normal SAP defined as a Glaucomatous Hemifield Test within normal limits (WNL); and pattern standard deviation (PSD) within 95% confidence interval (CI) limits. Inclusion criteria for the glaucoma group consisted of glaucomatous optic neuropathy defined as neuroretinal rim narrowing to the optic disc margin, notching, excavation, or RNFL defect; and corresponding abnormal visual field defined as abnormal Glaucoma Hemifield Test and pattern standard deviation (PSD) outside 95% normal limits. All glaucoma patients required one normal visual hemifield and the glaucomatous visual field damage had to be confined to a single hemifield. All patients had prior SAP experience and at least one confirmatory SAP examination for the hemifield damage. The apparently normal hemifield required having no test location worse than $p < 0.01$ on the pattern deviation (PD) plot. The glaucomatous hemifield required having a cluster of ≥ 3 contiguous test locations at $p < 0.05$ on the PD plot, with ≥ 1 test location at $p < 0.01$. The sensitivity of each test location was converted to the linear scale of 1/Lambert. The mean retinal sensitivity values in 1/Lambert were calculated in each hemifield using the average of 26/52 test locations.

Exclusion criteria common to both groups consisted of corneal or retinal pathology, and prior intraocular surgery except for uncomplicated cataract extraction or glaucoma procedures.

Subjects with ocular disease other than glaucoma or cataract, parapapillary atrophy extending to 1.7 mm from the center of the optic disc, unreliable visual field, or poor quality RBF, ONH or RNFL images were excluded. Patients with diabetes mellitus and systemic hypertension were included unless they were diagnosed with diabetic retinopathy or hypertensive retinopathy. Only one eye per subject was included.

All patients underwent a baseline examination consisting of a complete ophthalmic examination including slit lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, ultrasound pachymetry, dilated stereoscopic examination and photography of the optic disc, SAP, RBF measurement using Doppler SDOCT, and RNFL and GCC thickness measurements using SDOCT (RTVue-100; Optovue Inc., Fremont, CA, USA). The IOP and blood pressure measurements were performed at the same visit. Each SDOCT measurement was repeated twice at each session and the best quality image defined as having a signal strength index (SSI) ≥ 40 with no segmentation error was selected for the analysis. Mean ocular perfusion pressure (MOPP, in mmHg) was defined as the difference between 2/3 of mean arterial pressure and IOP.[5] At the time of the study, each glaucoma patient was under treatment at the discretion of the attending physician. Structural parameters included in the study were average, superior and inferior RNFL and GCC thickness values.

Doppler Spectral-domain Optical Coherence Tomography for Retinal Blood Flow Measurements

Doppler SDOCT employs Doppler technique in SDOCT imaging, and is based on the principle that moving particles, such as red blood cells inside a blood vessel, cause a Doppler frequency shift (Δf) to the light scattered based on the following equation:

$$\Delta \mathrm{f} = -2V_n \frac{Cos\theta}{\lambda_0}$$

Where V is the velocity vector of the moving particles; θ is the angle between the scanning beam and the flow direction; n is the refractive index of the medium, and λ_0 is the center wavelength of the light. In Doppler SDOCT, Doppler frequency shift introduces a phase shift in the spectral interference pattern that is captured by the line camera. With Fast Fourier transformation, the transform result is a complex function characterized by amplitude and phase. Structural information can be obtained via the amplitude result. The phase difference between sequential axial scans at each pixel is calculated to determine the Doppler shift. Therefore, in addition to structural imaging, Doppler SDOCT can be used to quantify blood flow parameters.[15] The Doppler SDOCT device used for the RBF measurements in this study was a spectrometer-based SDOCT (RTVue-100; Optovue Inc., Fremont, CA, USA). The system has a wavelength of 840 nm, an axial resolution of 5 μm and a transverse resolution of 20 μm in tissue. The time interval between two sequential axial scans is 36.7 μs. The maximum measurable Doppler shift is 13.6 kHz at the phase wrapping limit of ± π radian phase shift between sequential axial scans, corresponding to a maximum measurable axial velocity component of 4.2 mm/s in the eye.[15,16] The repeatability of total retinal blood flow, measured as the coefficient of variation, was 10.9% in the normal group, and 14.3% in the diseased eyes consisted of eyes with glaucoma, diabetic retinopathy and branch retinal vein occlusion.[17]

Doppler Image Acquisition and Processing

The pupils were dilated using 1% tropicamide and 2.5% phenylephrine eye drops. Doppler imaging was performed using a double circular scan pattern around the optic disc. The double-circular scan pattern consists of two concentric circles around the optic nerve head, with an inner ring diameter of 3.40 mm and an outer ring diameter of 3.75 mm.[5] This pattern transects all branch retinal arteries and veins emanating from the optic nerve head. The pattern is performed 6 times consecutively over 2 seconds so that blood flow measurement can be averaged over approximately 2 cardiac cycles.[4]

An experienced grader at the Doheny Doppler SDOCT Reading Center calculated the RBF using semi-automated software that has been previously described.[15,16] Blood vessels were identified based on Doppler and reflectance OCT images. The determination of vein versus artery was based on the comparison between the SDOCT images and color fundus photographs of the disk. Vessel diameter (D) was measured by using a caliper on the cross-sectional Doppler SDOCT images and lumen area ($\pi D^2/4$) was subsequently calculated. The venous cross-sectional areas for all branch vessels around the optic disc were averaged to obtain the average venous cross sectional area for the eye. The Doppler angle between the SDOCT beam and the direction of vessel was calculated using relative position of each vessel in the two concentric SDOCT images. Eye movement had minimal effect on the calculation of Doppler angle because of the short time interval between the inner and outer circular scans (0.16 second). Flow velocity was computed from the Doppler shift and Doppler angle; with steps to account for the effect of background retinal motion and transverse scan step size.[15] Veins were identified by the flow direction toward the optic disc. The volumetric blood flow rate for each pixel was calculated by multiplying the velocity by vessel area. Flow within a vein was calculated by summing the flow in the pixels over lumen cross-section. Flow measurements were averaged over each 2-second recording. For each vessel of each scan, a validation was applied based on the coefficient of variation of Doppler angle.

Measurements from all valid scans were averaged. Total RBF was calculated by summing flow from all detectable veins. Since the ocular circulation is a closed circulatory system and inflow must equal outflow in any steady state system that obeys the law of conservation of mass, it was assumed that the blood flow in arteries and veins were equal.[15]

Statistical Analysis

Statistical analysis was performed using JMP software version 8.0.2 (SAS Inc., Cary, NC). The estimated sample size for an alpha level of 5%, and a power of 80% was 21 to detect a 13 μL/min difference with a standard deviation of 10% in the retinal blood flow of glaucoma patients compared with normal controls, using the mean difference values provided by Wang and colleagues.[17] The distribution of data was examined using Shapiro-Wilk W Test of normality. One-way analysis of variance (ANOVA) was used for the comparison between groups and hemifields, and Tukey-Kramer HSD posthoc test was applied to correct for multiple comparisons. Logistic regression analysis was conducted to examine the impact of using topical and systemic medications, vitamins and food supplements, on the total and hemispheric RBF in normal and glaucoma patients. Multivariate regression analyses were performed to examine the associations between different variables in each visual hemifield and the RBF values in the corresponding hemispheres in glaucomatous and normal eyes.

Results

Thirty glaucomatous eyes of 30 glaucoma patients and 27 normal eyes of 27 normal subjects were included in this analysis. The retinal sensitivity in the apparently normal hemifield of glaucomatous eyes (28.5 ± 2.1dB; 774.9 ± 322.2 1/Lambert) was significantly lower than the retinal sensitivity in the abnormal hemifield of glaucomatous eyes (22.5 ± 7.1 dB, $p < 0.001$; 370.8 ± 317.7 1/Lambert; $p < 0.001$); and was reduced compared to the mean retinal sensitivity of the healthy eyes but did not reach a statically significant level (29.4 ± 1.6dB, $p = 0.07$; 935.6 ± 327.4 1/Lambert; $p = 0.07$).

Table 1 describes the demographics of the study population. Normal (65.4 ± 9.0 years) and glaucoma (61.5 ± 9.2 years; $p = 0.10$) groups did not have a statistically significant difference in age. The treated IOP in the glaucomatous eyes (14.2 ± 3.9mmHg) was similar to the untreated IOP in the normal eyes (13.9 ± 2.3mmHg; $p = 0.74$). The prevalence of

diabetes mellitus and systemic antihypertensive treatment was similar between the two groups (Table 1). Age was not associated with total RBF ($r = -0.11$, $p = 0.58$), average RNFL thickness ($r = 0.21$, $p = 0.27$), or average GCC thickness ($r = -0.06$, $p = 0.75$) in glaucomatous eyes. The total and hemispheric RBF, venous cross sectional area, and arteriolar cross sectional area were significantly reduced in glaucomatous eyes compared with normal eyes but venous blood flow velocity was similar between the two groups (Table 2). In glaucoma group, the systolic blood pressure was not associated with the RBF in the normal ($r = 0.03$; $p = 0.89$) or abnormal hemisphere ($r = 0.19$; $p = 0.35$). Similarly, the diastolic blood pressure was not associated with the RBF in the normal ($r = -0.33$; $p = 0.11$) or abnormal hemisphere ($r = -0.003$; $p = 0.99$). The MOPP was not associated with the RBF in the normal ($r = -0.23$; $p = 0.25$) or abnormal hemisphere ($r = -0.13$; $p = 0.52$).

The full list of the topical and systemic medications including food supplements has been provided in Table 3. Logistic regression analysis was conducted to examine the impact of using topical and systemic medications, vitamins and food supplements, on the total and hemispheric RBF, and total venous cross-sectional area in normal and glaucoma patients. The results showed that none of the topical and systemic medications and supplements used by the subjects in this study was associated with total or hemispheric RBF, or total venous cross-sectional area ($p > 0.05$) in normal or glaucomatous eyes.

Table 4 demonstrates the associations between the RBF, and RNFL and GCC thickness values and the retinal sensitivity in corresponding hemispheres and hemifields. The reduced RBF in the abnormal hemisphere was significantly associated with the thinner RNFL and GCC in the same hemisphere but there was no significant association between these parameters in the normal hemisphere. We did not find any significant association between RBF and retinal sensitivity in either hemisphere, and its corresponding hemifield.

In the glaucoma group, 15 eyes had perimetric abnormalities in the superior hemifield and 15 eyes had abnormalities in the inferior hemifield. Nine glaucoma patients had arterial hypertension under treatment and two glaucoma patients had controlled diabetes, one of whom also had arterial hypertension. The RBF, and RNFL and GCC thickness values in the hemisphere corresponding to the abnormal hemifield were all significantly reduced compared with the opposite hemisphere in glaucomatous eyes (Table 5). We also compared the values in the hemisphere with apparently normal visual field in glaucomatous eyes with the average of two hemispheres in the normal eyes. We found that the RBF, RNFL and GCC values were all significantly reduced in the hemisphere with apparently normal visual field of the glaucomatous eyes compared with the mean hemispheric values of the normal eyes. The arteriolar cross sectional area in the retinal hemisphere corresponding with the normal hemifield of glaucomatous eyes was 0.014 ± 0.005 mm^2; which was significantly ($p = 0.02$) reduced compared with the average of the superior and inferior arteriolar cross sectional area in the normal eyes (0.019 ± 0.004 mm^2). In 28 out of 30 glaucomatous eyes, the RBF in the hemisphere with apparently normal visual field was below the 0.5 percentile (28.74μL/min) of the RBF in the normal eyes.

Discussion

Several studies have demonstrated that vascular factors contribute to the development and progression of glaucomatous optic neuropathy.[1–5] It has been shown that attenuation of retinal vessels is associated with structural loss in glaucoma, which could be independent of systemic vascular risk factors and IOP.[12,13] It has been suggested that vascular factors are associated with the apoptosis of RGCs and development and progression of glaucomatous damage[1,2]; and that the mechanical compression of the microvasculature at the level of lamina cribrosa may affect the perfusion of the optic nerve head (ONH), leading to RGC

ischemia and apoptosis.[21,22] Other studies have shown that retinal vessels might be involved in the pathogenesis of glaucoma.[11,23,24]

It is unclear whether the retinal vascular changes are primary or secondary in glaucoma. One plausible hypothesis refers to the fact that when the demand is diminished the supply is also reduced.[25,26] Another hypothesis states that the loss of RGCs may affect regional oxygen demand, or the need of vascular supply in the corresponding superficial retinal area, which would trigger the retinal vascular adjustment via autoregulatory mechanisms.[12,13] It has been shown that the retinal vascular contribution to the total peripapillary RNFL thickness may increase with glaucoma progression.[27] A combined model of primary and secondary insults in glaucoma has been proposed by Chercheanu et al.[28] The primary insult appears to occur at the ONH, with increased IOP and ischemia affecting RGC axons at the post-laminar region. The biomechanical properties of the tissue and CSF pressure would interact as the modulating factors, preparing the background for the secondary insults. The secondary insults may occur if the perfusion pressure falls below the lower limit of autoregulation or if neurovascular coupling fails. The vascular endothelial dysfunction and impaired astrocyte-vessel signaling might also be responsible at this stage.[28] It has been proposed that the retinal vessels are not only under the control of the vascular endothelial cells, but additionally under the control of the neural and glial cells.[10] Autoregulation of ocular blood flow (OBF) compensates for varying perfusion pressures, adapts to the retinal activity (neurovascular coupling), and maintains the posterior segment at a constant temperature.[10] It has been hypothesized that if regulation does not occur according to the needs of the tissue, vascular dysregulation occurs.[10] Patients with disturbed autoregulation tend to have unstable ocular blood flow, which in turn, may provoke reperfusion injury, leading to oxidative stress and glaucomatous optic neuropathy.[10] Using a mouse model of glaucoma, it has been shown that ischemia and reperfusion injury resulted in RGC death within 48 hours and degenerated capillaries within a week, indicating that capillary degeneration is an unrecognized component of acutely elevated IOP and develops only after neurodegeneration is severe.[26] This finding raises the possibility that damage to the neural retina contributes to capillary degeneration, secondary to the RGCs death. Recently a relationship between retinal venous caliber, IOP and cerebrospinal fluid (CSF) pressure has been noted, with the degree of retinal venous caliber being associated with the translaminar pressure gradient.[29]

In the present study, we observed that RBF, RNFL, and GCC were reduced in the normal hemisphere of glaucomatous eyes compared with the mean hemispheric values in the normal eyes. There have been previous reports of reduced RBF in glaucoma[12,13]; however, to the best of our knowledge, this is the first report of reduced retinal blood flow in the hemisphere with apparently normal visual field of glaucomatous eyes with single hemifield damage. The finding of early structural loss in the hemisphere with apparently normal visual field is consistent with the literature that demonstrates that eyes with SAP defects confined to a single hemifield have evidence of diffuse attenuation in RNFL, macular thickness and retinal sensitivity in apparently normal areas of the visual field.[30–32]

In the current study, the glaucoma group happened to have lower systemic blood pressure. It might be considered as a limitation from the Study Design perspective. However, in reality lower systemic blood pressure led to lower MOPP in the glaucoma group, who had reduced RBF. In our study the blood velocity did not differ between the two groups significantly; however, the vessel caliber was significantly reduced in the glaucomatous eyes. The RBF is the product of retinal blood vessel cross sectional area times blood velocity. Since the velocity did not differ between the two groups, the reduced RBF was presumably due to reduced retinal vessel caliber, as we observed. This finding is in agreement with previous studies that reported attenuation of retinal vessels in glaucoma.[11,14,53] However, the association between glaucomatous progression and retinal vessel diameter is still

controversial.[33] Our finding that RBF and vessel diameter were significantly reduced in glaucoma independently of the patient's age, agree with the findings of Jonas and colleagues who found that the vessel diameters decreased significantly with increasing glaucoma stage independently of the patients' age.[11] It should be considered that open angle glaucoma is an age-related disease; however, the rate of retinal nerve fiber layer or ganglion cell complex loss due to glaucoma might be much faster and not proportional to the rate of aging in glaucoma subjects. Also there is a great chance that the RBF is compromised in glaucoma subjects due to factors other than glaucoma, such as atherosclerosis or other comorbidities, and therefore, the association between RBF and glaucoma is not straightforward either.

The impact of ageing on ocular blood flow is through the change in vasculature tone and some degree of endothelial dysregulation leading to a rise in systolic blood pressure, which causes an increase in mean ocular perfusion pressure (MOPP). The autoregulatory capability of the retinal vasculature in normal ageing is the main determinant at this stage. If the glaucoma progression is accelerated compared with progressing age, the decreased RBF in glaucoma progression and in progressing ageing will not be concordant. This question was not the intent of the present study but it is an excellent hypothesis for further studies using a longitudinal study design.

The Blue Mountains Eye Study included 3654 participants and found that retinal arteriolar attenuation was associated with long-term risk of open angle glaucoma, and demonstrated that early vascular changes are involved in the pathogenesis of glaucoma.[11] The Singapore Malay Eye Study with 3019 participants found a significant association between the attenuation of retinal arteriolar and venular caliber changes with glaucomatous optic neuropathy, independent of intraocular pressure.[14] Our findings agree with these large studies.

Various studies have shown associations between structural loss and retinal vascular change in glaucomatous eyes.[12,35] Consistent with previous studies,[36–38] we detected glaucomatous structural loss in RNFL and GCC of glaucomatous eyes, significantly associated with the RBF in the hemisphere corresponding to the abnormal hemifield. Certainly there is evidence that the relationship between glaucomatous structure and function is highly complex and in part dependent upon the severity of glaucoma. The relationship between structure and RBF is equally complex and may or may not be associated with on another. More studies are required to address this important question.

Of interest, our results demonstrate no relationship between RBF and retinal sensitivity in the corresponding abnormal hemisphere and hemifield. Previous studies have reported conflicting results with regard to an association between the retinal blood flow and visual field abnormalities in patients with POAG.[39–41] Some studies examined this association in the entire retina[41], and some in each hemifield separately,[39] and yet, neither one was able to report a significant association between RBF and glaucomatous field damage in POAG patients.[39,41] To examine the associations between RBF and function in the normal and abnormal hemispheres, we converted individual retinal sensitivity values of each visual field to the linear scale of 1/Lambert to circumvent the nonlinearity of the decibel scale. This conversion made all ranges of loss uniformly consistent across all stages of disease. Hwang et al.[4] converted all structural parameters and RBF measures to logarithmic scale of dB and found a significant association between the RBF and visual field mean deviation (MD), but inconsistent relationships between RBF and glaucomatous structural measures. Dissimilarities in the study population, stage of disease, local metabolic variables that regulate blood flow, and systemic factors including blood pressure and antihypertensive therapy may also contribute to observed differences between these two studies. The special value of the current hemispheric study compared with the global analysis of Hwang and

colleagues[4] is that our study rules out the effect of global confounders that act on both hemispheres such as glaucoma medication, blood pressure medication, IOP, or blood pressure. It has been shown that attenuation of retinal vessels is associated with structural loss in glaucoma, which could be independent of systemic vascular risk factors and intraocular pressure (IOP).[12,13] These findings emphasize the complex relationship between vascular physiologic mechanisms that regulate ocular blood flow and glaucomatous optic neuropathy. Longitudinal studies are necessary to further explore the relationship between impaired autoregulation, RGC survival, and visual function.

Several Doppler OCT methods have been used to measure the blood velocity for the calculation of retinal blood flow. Each method has its own strengths and shortcomings. One of these approaches calculates the angle between the scanning beam and the flow direction from structural OCT tomograms using registered 3D images. This method is not accurate for vessels that are close to perpendicular to the incident beam.[42,43] In the second approach, the flow is measured directly from *en face* cross sections, and is not angle dependent and leads to a direct value of the absolute flow. It requires a high-speed OCT platform but even at high speed, the vessels within the volume are scanned consecutively and might exhibit different cardiac pulse phases.[44] In the third approach, the 3D velocity vector is measured using simultaneous multi-beam illumination of the same sample point from different angles. This technique is complex but is not ideal for retinal imaging. The sensitivity of each beam is reduced to decrease the total illumination power to the eye for laser safety considerations. The overlap of several beams on the retina, required for accurate velocity calculation, is challenging. The absolute velocity cannot be calculated if the incidence plane is perpendicular to the flow direction in the *en face* projection.[45] In the fourth method, a flexible scanning dual beam bidirectional system is used. The system is based on high-speed swept source technology that allows measuring higher flow velocity, closer to the ONH. The velocity is extracted independent of the vessels orientation and angle. This technique has limited precision due to the small angular separation between the two beams.[46] In the last method, which was used in our study, the vessel angle is extracted from double circular scans at different scan radii. Using the dual scan beam helps with more accurate determination of the vessel angle. This method is sensitive to eye movement but the motion artifact can be removed using proper 3D registration to provide a correct reference volume.[15]

Our study has limitations. We were only able to measure the total and hemispheric RBF in a group of mild to moderate glaucomatous eyes with single hemifield damage but we were not able to measure the localized RBF confined to areas smaller than retinal hemisphere. This technology does not measure the microcirculation of the ONH and neuroretinal rim. The Doppler OCT blood flow measurements have been reported to have reasonably good reproducibility, with intraclass correlation coefficients (ICC) of 0.93 for repeat measurements.[16] The repeatability of total retinal blood flow, measured as the coefficient of variation, was 10.9% in the normal group, and 14.3% in the diseased eyes consisted of eyes with glaucoma, diabetic retinopathy and branch retinal vein occlusion.[17] The variability of this technology may still be improved. Doppler SDOCT measures the retinal venous blood flow velocity but not arterial velocity because arterial velocity often exceeds the detection range of the device. However, since retinal circulation is a closed circulatory system, the total amount of flow in retinal veins is assumed to be equal to the total amount of flow in retinal arteries. One of the technical limitations of the study was the use of semi-automated grading and calculation technique for blood flow measurements. This method is tedious and time consuming. Recent advancements are underway to circumvent the semi-automated technique to a fully automated method. Moreover, the role of a grader makes the calculations susceptible to the grader’s potential subjective errors.

The concomitant use of topical and systemic medications during the course of this study could potentially affect the RBF. Few studies have examined the impact of systemic medications and supplements on retinal blood flow in glaucoma patients with controversial results.[47] Topical glaucoma medications reduce the IOP and may indirectly increase the MOPP. An increase in MOPP does not necessarily lead to an increase in RBF because the retinal circulation has autoregulatory mechanisms, unless the perfusion pressure falls below the lower limit of autoregulation, or the neurovascular coupling fails.[10]

Some reports have indicated that topical carbonic anhydrase inhibitors increase retinal blood flow in glaucoma patients, and improve retinal vascular autoregulation due to blockade of carbonic anhydrase and an increase in CO2 concentration in local tissues, resulting in vascular dilation and increased blood flow.[48,49] There are some evidences that show some calcium channel blockers, adenosine, histamine, estrogens, and nitric oxide precursors such as L-arginine may increase ocular blood flow in general; and alpha-2 adrenergic agonists may decrease the RBF.[47] Overall, we did not find any significant association between total or hemispheric retinal blood flow, and topical and systemic medications and dietary supplements used in this study, as it was demonstrated in Table 3, which might be potentially due to small sample size.

The impact of topical mydriatic agents on ocular hemodynamic parameters might be considered as a confounding factor. We recently published a paper regarding the impact of topical mydriatic ophthalmic solutions on retinal vascular reactivity and blood flow in normal eyes.[50] We found that the three commonly used mydriatic agents did not differentially influence the retinal blood flow of the major retinal arterioles in normal eyes. In the current study all subjects were dilated using 1% tropicamide and 2.5% phenylephrine eye drops; therefore, the same dilating agent influenced ocular hemodynamics in all subjects similarly should it have any impact on the retinal blood flow. Moreover, since glaucoma is associated with autonomic and regulatory dysfunction, one cannot exclude the effect of dilating agents on either the glaucoma patients or on the abnormal hemifield. Studying such effect in glaucoma population is the subject of another major experimental undertaking.

In conclusion, in glaucomatous eyes with single-hemifield damage, the RBF was reduced in the hemisphere corresponding to the abnormal hemifield; and the reduced RBF was associated with thinner RNFL and GCC thicknesses in the corresponding hemisphere. The retinal blood flow in the hemisphere with apparently normal visual field was reduced compared with the mean hemispheric flow values in the healthy eyes. These findings suggest that glaucoma is associated with vascular changes in the retina.

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Table 1

Clinical characteristics of the study population.

	Normal (n = 27)	Glaucoma (n = 30)	p-value
Age (years)	65.4 ± 9.0	61.5 ± 9.2	0.10*
Gender (Male/Female)	6/21	12/18	0.14‡
IOP (mmHg)	13.9 ± 2.3	14.2 ± 3.9	0.74*
SBP (mmHg)	130.0 ± 15.3	119.5 ± 11.6	0.009*
DBP (mmHg)	81.2 ± 8.9	74.7 ± 8.0	0.009*
MOPP (mmHg)	51.1 ± 6.7	46.1 ± 6.8	0.01*
Diabetes Mellitus (Yes/No)	1/26	1/29	0.99‡
SAP MD (dB)	−0.2 ± 1.3	−3.9 ± 3.8	<0.001*
SAP PSD (dB)	1.5 ± 0.5	5.2 ± 4.0	<0.001*

*One-way analysis of variance (ANOVA) with Tukey-Kramer Honestly Significant Difference (HSD) posthoc test (JMP 8.0.2);

‡Fisher's exact test;

IOP = intraocular pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; MOPP = mean ocular perfusion pressure; SAP = standard automated perimetry; MD = mean deviation; dB = decibel; PSD = pattern standard deviation.

Table 2

The comparisons between normal and glaucomatous eyes for retinal blood flow, retinal nerve fiber layer thickness and ganglion cell complex thickness.

	Normal (n = 27)	Glaucoma (n = 30)	p-value*
Total Retinal Blood Flow (μL/min)	46.5 ± 10.6	34.6 ± 12.2	<0.001
Superior Retinal Blood Flow (μL/min)	24.5 ± 8.2	17.7 ± 5.6	<0.001
Inferior Retinal Blood Flow (μL/min)	21.9 ± 5.6	16.7 ± 8.7	0.01
Average venous cross sectional area (mm^2)	0.052 ± 0.012	0.039 ± 0.009	<0.001
Superior venous cross sectional area (mm^2)	0.028 ± 0.008	0.020 ± 0.005	< 0.001
Inferior venous cross sectional area (mm^2)	0.024 ± 0.007	0.019 ± 0.005	< 0.001
Average venous blood flow velocity (mm/s)	15.0 ± 2.3	13.7 ± 6.3	0.30
Average arteriolar cross sectional area (mm^2)	0.036 ± 0.009	0.028 ± 0.008	0.002
Superior arteriolar cross sectional area (mm^2)	0.020 ± 0.005	0.015 ± 0.007	0.04
Inferior arteriolar cross sectional area (mm^2)	0.017 ± 0.004	0.012 ± 0.004	0.007
Average RNFL (μm)	101.0 ± 6.6	85.0 ± 15.5	<0.001
Superior RNFL (μm)	123.6 ± 13.7	94.2 ± 20.9	<0.001
Inferior RNFL (μm)	126.1 ± 11.6	96.4 ± 23.2	<0.001
Average GCC (μm)	96.1 ± 5.7	80.6 ± 10.3	<0.001
Superior GCC (μm)	95.6 ± 5.0	82.2 ± 9.8	<0.001
Inferior GCC (μm)	96.7 ± 6.7	79.0 ± 12.8	<0.001

* One-way analysis of variance (ANOVA) with Tukey-Kramer Honesty Significant Difference (HSD) posthoc test (JMP 8.0.2);

RNFL = retinal nerve fiber layer thickness; GCC = ganglion cell complex thickness.

Table 3

The complete list of the topical and systemic medications including food supplements. Logistic regression was conducted to evaluate the impact of using medications on total retinal blood flow.

Medications	Glaucoma (n = 30)	Odds ratio per μL/min total RBF (p-value)*	Normal (n = 27)	Odds ratio per μL/min total RBF (p-value)*
Systemic beta blockers	7	1.00 (0.82)	4	0.91 (0.09)
Calcium channel blockers	2	0.98 (0.76)	1	0.88 (0.22)
Diuretics	1	0.95 (0.48)	2	0.97 (0.70)
Anti-platelets	9	0.94 (0.11)	1	1.09 (0.49)
Diabetes medications	3	0.90 (0.16)	1	1.09 (0.49)
Vitamin and mineral supplements	4	0.96 (0.30)	1	1.05 (0.68)
Food Supplements	3	1.00 (0.53)	0	N/A
Anti-lipids	8	0.90 (0.10)	1	1.09 (0.49)
Anti-histamines	1	0.93 (0.29)	0	N/A
Selective serotonin re-uptake inhibitors	1	0.93 (0.29)	0	N/A
Angiotensin-converting-enzyme inhibitor	0	N/A	2	1.00 (0.98)
Angiotensin II receptor blockers	3	1.00 (0.87)	0	N/A
Hypothyroidism medications	1	1.10 (0.49)	0	N/A
Asthma medications	2	0.80 (0.13)	1	1.07 (0.58)
Estrogen	0	N/A	1	1.05 (0.68)
Pacemaker	0	N/A	1	1.12 (0.41)
Topical beta blockers	11	1.00 (0.93)	0	N/A
Prostaglandin analogs	16	1.00 (0.83)	0	N/A
Alpha 2-adrenergic agonists	3	0.99 (0.98)	0	N/A
Nonselective adrenergic agonists	1	1.58 (0.29)	0	N/A
Topical or systemic				
carbonic anhydrase inhibitors	7	0.97 (0.38)	0	N/A

RBF = retinal blood flow; N/A = not applicable;

*Logistic regression analysis (JMP 8.0.2).

Table 4

Hemispheric Correlation Between Retinal Blood Flow and Other Diagnostic Parameters in the Glaucoma Group.

Variable	By Variable	Abnormal Hemifield and Corresponding Abnormal Hemisphere		Normal Hemifield and Corresponding Normal Hemisphere	
		r	p-value	r	p-value
Retinal Blood Flow (μL/min)	RNFL (μm)	0.41	0.02	0.30	0.10
	GCC (μm)	0.43	0.02	−0.02	0.92
	Retinal sensitivity (1/Lambert)	0.31	0.09	−0.09	0.63

* Multivariate regression analysis (JMP 8.0.2);

RNFL = retinal nerve fiber layer thickness; GCC = ganglion cell complex thickness.

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Table 5

The Comparisons Between Normal and Abnormal Hemifields of Glaucomatous Eyes; and Normal Hemifield of Glaucomatous Eyes with Mean Hemispheric Values of Normal Eyes.

Parameters	Glaucoma			Normal	p-value*
	Abnormal Hemisphere	Normal Hemisphere	p-value	Mean Hemispheric	
Retinal Blood Flow (μL/min)	15.3 ± 5.4	19.3 ± 8.4	0.03	23.2 ± 5.3	0.04
RNFLT (μm)	87.0 ± 20.2	103.7 ± 20.6	0.002	124.8 ± 9.6	<0.001
GCC (μm)	77.6 ± 12.1	83.6 ± 10.1	0.04	96.1 ± 5.7	<0.001

One-way analysis of variance with Tukey-Kramer Honestly Significant Difference (HSD) posthoc test (JMP 8.0.2). The retinal blood flow, retinal nerve fiber layer thickness and ganglion cell complex in normal and abnormal hemispheres of glaucomatous eyes were compared. The normal hemisphere of the glaucomatous eyes was then compared with the mean of the two hemifields in the normal eyes. The p-values marked by the asterisk sign (*) demonstrate the results for the latter comparison.