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Deep Retinal Layer Microvasculature Dropout detected by the Optical Coherence Tomography Angiography in Glaucoma

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Abstract

Purpose—To investigate factors associated with dropout of the deep retinal layer microvasculature within the β -zone parapapillary atrophy (β PPA) assessed by optical coherence tomography angiography (OCT-A) in glaucomatous eyes.

Design—Cross-sectional study.

Participants—Seventy-one eyes from 71 primary open angle glaucoma (POAG) patients with β PPA enrolled in the Diagnostic Innovations in Glaucoma Study.

Methods— β PPA deep layer microvasculature dropout was defined as a complete loss of the microvasculature located within deep retinal layer of the β PPA from OCT-A-derived optic nerve head vessel density maps by standardized qualitative assessment. Circumpapillary vessel density (cpVD) within the retinal nerve fiber layer (RNFL) was also calculated using OCT-A. Choroidal thickness and presence of the focal lamina cribrosa (LC) defect were determined using swept-source OCT.

Main Outcome Measures—Presence of the β PPA deep layer microvasculature dropout. Parameters including age, systolic and diastolic blood pressure, axial length, intraocular pressure,

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Needs Conflict of interest statement for everyone.

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disc hemorrhage, cpVD, visual field (VF) mean deviation (MD), focal LC defect, β PPA area, and choroidal thickness were analyzed.

Results— β PPA deep layer microvasculature dropout was detected in 37 eyes (52.1%) of eyes with POAG. Eyes with dropouts had a higher prevalence of LC defect (70.3 vs. 32.4%), lower cpVD (52.7 vs. 58.8%), worse VF MD (-9.06 vs. -3.83dB), thinner total choroidal thickness (126.5 vs. 169.1/ μ m), longer axial length (24.7 vs. 24.0mm), larger β PPA (1.2 vs. 0.76mm²) and lower diastolic blood pressure (74.7 vs. 81.7mmHg) than those without dropouts ($P < 0.05$, respectively). In the multivariate logistic regression, higher prevalence of focal LC defect (odds ratio [OR], 6.27; $P = 0.012$), reduced cpVD (OR, 1.27; $P = 0.002$), worse VF MD (OR, 1.27; $P = 0.001$), thinner choroidal thickness (OR, 1.02; $P = 0.014$), and lower diastolic blood pressure (OR, 1.16; $P = 0.003$) were significantly associated with the dropout.

Conclusions—Certain systemic and ocular factors such as focal LC defect, more advanced disease status, reduced RNFL vessel density, thinner choroidal thickness, and lower diastolic blood pressure were factors associated with the β PPA deep layer microvasculature dropout in glaucomatous eyes. Longitudinal studies are required to elucidate the temporal relationship between β PPA deep layer dropout and these factors.

A potential pathogenic role for the microvasculature and ocular blood flow in the development and progression of the glaucomatous optic neuropathy has long been recognized.^{1, 2} The deep retinal layer microvasculature within the parapapillary area is of particular clinical interest as it is downstream from the short posterior ciliary artery³⁻⁷, which also perfuses the deep optic nerve head (ONH) structures.⁵⁻⁷ Therefore, microvasculature within the β -zone parapapillary atrophy (β PPA) may be related to the vascular and mechanical properties of the deep structures such as prelaminar and laminar tissue. Moreover, there have been several reports that reduced choroidal vasculature may be related to the development of the glaucoma.^{3, 8} However, in-vivo visualization of the β PPA deep layer microvasculature has been problematic. Previous investigations had to rely on invasive imaging modalities such as fluorescein angiography or Indocyanine green angiography (ICGA) that could not distinguish this layer.^{3, 4}

With the recent development of optical coherence tomography angiography (OCT-A) noninvasive in-vivo imaging of the microvasculature located within various retinal layers is possible.^{9-11, 12} There are a limited number of studies documenting the sparser microvasculature in the retinal nerve fiber layer (RNFL) in eyes of glaucoma patients, compared to glaucoma suspects and healthy subjects.¹² However, little is known about the visualization of the deep layer microvasculature within the β PPA area.

The purpose of this study is to characterize dropout of the deep retinal layer microvasculature within the β PPA in primary open angle glaucoma (POAG) patients. In addition, the relationship between the dropout and the clinical characteristics such as glaucoma severity, focal lamina cribrosa (LC) defect, and choroidal thickness was investigated.

Materials and Methods

POAG patients from the Diagnostic Innovations in Glaucoma Study (DIGS) (ClinicalTrials.gov identifier: NCT00221897) were included. Details of the DIGS protocol and eligibility have been described previously.¹³ This study was approved by the Institutional Review Board at the University of California, San Diego and conformed to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA). Informed consent was obtained from all participants.

Study Subjects

Established POAG patients with confirmed β -zone parapapillary atrophy (β PPA) from standardized photographic assessment who completed OCT-A imaging and ONH imaging using both spectral-domain OCT (SD-OCT) and swept-source OCT (SS-OCT) were enrolled. All subjects received an ophthalmological examination, including assessment of best corrected visual acuity (BCVA), refractive error, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy, central corneal thickness (CCT) measured with ultrasound pachymetry (DGH Technology Inc. Exton, PA), axial length measured by the IOL Master (Carl Zeiss Meditec, Dublin, CA), dilated fundus examination, simultaneous stereophotography of the optic disc, standard automated perimetry (Humphrey Field Analyzer; 24-2 Swedish interactive threshold algorithm; Carl-Zeiss Meditec), SD-OCT, OCT-A, and SS-OCT. Perimetry and all imaging tests were conducted within a 6-month period.

Systolic and diastolic blood pressure (BP) and pulse rate were measured twice with an Omron Automatic (Model BP791IT) blood pressure instrument, and the mean values used in the analysis. Mean arterial pressure was derived as $1/3$ systolic BP + $2/3$ diastolic BP. Mean ocular perfusion pressure (MOPP) was calculated as the difference between $2/3$ of mean arterial pressure and IOP.

Presence of optic disc hemorrhage and β PPA was determined based on optic disc stereophotographs obtained at the participants' annual dilated examination. Glaucomatous optic disc hemorrhage was defined as an isolated splinter or flame-shaped hemorrhage on optic disc tissue or crossing the optic disc.¹⁴ β PPA was defined as an atrophy of the retinal pigment epithelium (RPE), and visibility of the large choroidal vessels and the sclera.^{15, 16} Two independent observers masked to patient information and test results independently evaluated each image. Discrepancies between the two observers were resolved by consensus. To be included, subjects were required to have been diagnosed as POAG, to be > 18 years old, to have BCVA $\geq 20/40$, and to have open angle by gonioscopy. Subjects with a history of ocular intervention (except for uncomplicated cataract or glaucoma surgery), intraocular diseases (e.g. diabetic retinopathy or non-glaucomatous optic neuropathy), or systemic diseases (e.g. stroke or pituitary tumor) that could influence the study results were excluded. Those with systemic hypertension and diabetes mellitus were included unless they were diagnosed to have diabetic or hypertensive retinopathy. Subjects with unreliable visual field (VF) or poor quality imaging tests were also excluded.

POAG was defined as the presence of glaucomatous optic nerve damage (i.e., the presence of focal thinning, notching, localized or diffuse atrophy of retinal nerve fiber layer) based on standardized assessment of simultaneous stereophotographs, and associated repeatable VF damage. Glaucomatous VF damage was defined as a VF outside normal limit on glaucoma hemifield test or pattern standard deviation outside 95 % normal limits confirmed on two consecutive, reliable (fixation losses and false negatives 33% and 15% false positives) tests.

Spectral-Domain Optical Coherence Tomography Imaging

All participants underwent ONH imaging with a commercially available SD-OCT system (Avanti; Optovue, Inc., Fremont, CA, USA) using a light source with a 70-kHz, axial line rate, and with a center wavelength of 840 nm. The ONH map protocol calculates disc area and circumpapillary RNFL (cpRNFL) thicknesses in a 10 pixel-wide band along a circle of 3.45 mm in diameter centered on the ONH based on 360 degree global area. Only good-quality images with a signal strength index ≥ 37 , and without segmentation failure or artifacts were included.¹²

Optical Coherence Tomography Angiography Imaging

The Angiovue (Optovue, Inc., Fremont, CA, USA) incorporated in the Avanti SD-OCT system provides a non-invasive visualization of the vascular structures of various user defined retinal layers by using Motion Contrast Technology (MCT) and Split-Spectrum Amplitude-Decorrelation Angiography (SSADA) method. Details have been described in elsewhere.^{9, 12, 17, 18} Briefly, the OCT-A image is based on an amplitude decorrelation between 2 rapidly repeated B-scans, and the SD-OCT image consists of the average of the 2 rapid repeats at the same B-scan location. In addition, the SSADA technique allows high-resolution 3D visualization of perfused retinal microvasculature. Image quality review was performed on all whole depth images according to a standard protocol established by the Imaging Data Evaluation and Analysis (IDEA) reading center. Trained observers reviewed scans and those with poor image quality, as defined by the following criteria, were excluded: 1) a signal strength index < 48 (1 = minimum, 100 = maximum), 2) poor clarity 3) residual motion artifacts visible as irregular vessel pattern or disc boundary on the enface angiogram, 4) local weak signal, 5) segmentation errors of the RNFL and choroidal layer.¹² Scanning laser ophthalmoscopy (SLO) images of the Avanti SD-OCT centered on the optic disc acquired at the same positions as the OCT-A were also reviewed for the delineation of the disc margin and β PPA, as described below. Eyes with poor SLO images in which the β PPA or optic disc were not clearly delineated were also excluded.

Vessel density (%) of the microvasculature located in the RNFL layer was calculated as the proportion of measured area occupied by flowing or perfused blood vessels on the ONH images with a 4.5×4.5 mm field of view centered on the optic disc.¹² Two vessel density summary parameters in the RNFL were obtained: 1) whole image vessel density (wiVD) measured in the entire 4.5×4.5 mm image; 2) circumpapillary vessel density (cpVD) calculated in a region defined as a 750- μ m-wide elliptical annulus extending from the optic disc boundary based on 360 degree global area.^{12, 19}

Dropout of the Deep Retinal Layer Microvasculature in the β -zone Parapapillary Atrophy Region

β PPA on the SLO images was manually delineated by 2 observers as an area between the optic disc margin defined as the inner margin of the peripapillary scleral ring^{20, 21} and β PPA defined as the boundary of the RPE atrophy with visible large choroidal vessels and sclera.^{15, 16} β PPA area was automatically calculated in pixels using ImageJ software (ver. 1.48; <http://imagej.nih.gov/ij/download.html>, National Institutes of Health, Bethesda, MD).²² β PPA area was converted from pixels to millimeters squared by using Littmann's formula for each axial length to correct the ocular magnification in OCT.^{23, 24} Details of the formula was provided in elsewhere.²³ The Avanti SD-OCT has a default axial length of 23.95 mm and the anterior corneal curvature radius of 7.77 mm. The average β PPA area values of the two observers (M.H.S and P.C.M) masked to the clinical information was used.

Deep layer microvasculature within the β PPA area was evaluated on the 4.5×4.5 mm-sized choroidal layer vessel density maps of optic nerve head OCT-A images. Both optic nerve head OCT-A images and SLO images were acquired by centering on the optic disc (Fig 1). Deep layer microvasculature within the β PPA on the choroidal layer map is mostly composed of the choriocapillaris (Fig 1B), and vasculature within the elongated and thinned scleral flange devoid of choroid may be partly included in several eyes.²⁵ A dropout of the deep layer microvasculature within the β PPA was defined as a complete loss of the choriocapillaris or the microvasculature within the scleral flange on both horizontal and enface choroidal layer vessel density map (Fig 2, Fig 3 F and G). Dropout was required be present in at least 4 consecutive horizontal B-scans and also to be $200 \mu\text{m}$ in diameter in at least one scan. To avoid false negatives and positives due to reflectance or shadowing of the large vessels, minimal width of the dropout was required to be $200 \mu\text{m}$ based on the approximate width of the central retinal vein in glaucomatous eyes.^{26, 27} Reflectance or shadowing of the large vessels on the horizontal and enface images was also excluded from the qualitative analysis by the two independent observers (M.H.S and P.C.M) masked to the patients' baseline characteristics and optic disc features (Fig 2B). Discrepancies between the two observers were resolved by consensus, or, if consensus could not be reached, the subject was excluded from the analysis. If both eyes of a subject had microvasculature dropout or if neither of the two eyes had dropout, one eye was randomly selected for inclusion in the analysis. When microvasculature dropout was present in only one eye of a subject the eye with dropout was included in the analysis.

The sectoral location of the dropout was determined based on the eight 45 degree sectors corresponding to those on the RNFL vessel density map of the OCT-A (Fig 3 E and F). If the subject had microvasculature dropout located over more than one neighboring sectors, the sector that included the larger portion of a defect were assigned (Fig 3). In case of dropout that has more than 1 consecutive sector that was equally involved, all of those sectors were assigned.

Swept-Source Optical Coherence Tomography imaging

In addition, optic disc images were acquired with a SS-OCT instrument (DRI-OCT, Topcon, Tokyo, Japan) to determine the presence of the focal LC defect and to measure the choroidal

thickness. This device uses the light source with a center wavelength of 1050 nm, and has image-acquisition rate of 100,000 A-scans/second. Details on the device have been described elsewhere.²⁸⁻³⁰ A 3-dimensional (3D) raster scan protocol (wide-field protocol) consisting 256 serial horizontal B-scans was conducted over 12×9-mm cube centered on the posterior pole.^{28, 29} Serial enface images were obtained from the 3D data set.

Poor quality images with clipped or poorly focused scans, motion artifacts, quality score < 50, poorly visible LC, or the segmentation failure of the choroidal layer were excluded.^{28, 29} Poor visibility of the LC was defined as < 70% visibility of the anterior laminar surface within the BM opening.²⁹ Segmentation failure of choroid was defined as > 25 % discordance between the visual inspection and the automated identification of the BM and the choriocleral interface.²⁸

In determining the presence of focal LC defects, two independent observers (M.H.S and P.C.M) masked to the clinical information of the study subjects reviewed the horizontal and enface SS-OCT images. Discrepancies were resolved by consensus or, if consensus could not be reached, the subject was excluded from the analysis. Focal LC defects were defined as laminar holes or laminar disinsertions violating the normal U- or W-shaped contour of the anterior laminar surface.³¹⁻³⁷ Focal LC defects were required to be 100 μm in diameter and > 30 μm in depth in at least 2 consecutive scans.³¹⁻³⁵ The size criteria were established in previous studies to avoid false positive focal LC defect detection.³¹⁻³⁵ Observers also confirmed that the candidate LC defects did not correspond with the hypo-reflective vessel shadowing by comparing between the enface images and the disc photographs.³⁷ To determine the sectoral location of the LC defect, an 8-sector face circle was placed around the ONH of the SS-OCT enface image after matching its location with that of the AngiVue cpVD circular diagram by manually registering to the large vessels (Fig 3). Then, the sector in which the LC defect was located was assigned. If the subject had a LC defect located over two neighboring sectors, only the sector that included the larger portion of a defect was assigned.

Total choroidal thickness was derived from the average choroidal thickness values of the 108 1mm²-sized grid locations on the 12×9 mm wide-field SS-OCT images using SS-OCT software.²⁹ Accuracy of the choroidal segmentation was reviewed and scans with segmentation failures were excluded.

Data analysis

Clinical characteristics and OCT-A derived cpVD values were compared between eyes with and without β PPA deep layer microvasculature dropout. For continuous variables Student's *t*-test for independent samples or Mann-Whitney test was used depending on the whether the distribution of the values was normal based on Shapiro-Wilk tests. For categorical variables, chi-squared test was performed. Univariate logistic regression analysis was performed to identify parameters associated with the β PPA deep layer microvasculature dropout. Then, stepwise multivariate logistic regression was performed for those with a P value of < 0.10 in the univariate analysis. The kappa coefficient was calculated to evaluate inter-observer agreement in determining the β PPA deep layer microvasculature dropout and focal LC defects.^{38, 39} Inter-observer reproducibility of the measurement of the β PPA area was

measured by calculating the intraclass correlation coefficients of all included subjects. Analyses were conducted using MedCalc (MedCalc, Inc., Mariakerke, Belgium). The α level (type I error) was set at 0.05.

Results

Seventy-one eyes of 71 POAG patients are included in this report. Of the 103 eyes of 103 POAG patients that initially met patient eligibility criteria, 13 eyes were excluded due to poor quality OCT-A images, 3 eyes due to poor quality SLO images, 5 eyes due to poor quality SD-OCT ONH scan, and 10 eyes due to poor quality SS-OCT images. Among the remaining 72 eyes of 72 patients, 1 eye was excluded due to failure in reaching the consensus between the two observers for the determination of the deep layer microvasculature dropout. The 32 eyes that were excluded were similar to those included with respect to age, gender, spherical equivalent, axial length, CCT, ethnicity, presence of the diabetes and hypertension, and VF MD and PSD ($P > 0.05$) (data not shown).

Inter-observer agreement for determination of both microvasculature dropout and focal LC defects was excellent (Kappa = 0.86, 95 % CI 0.74–0.98, $P < 0.001$ and Kappa = 0.82, 95 % CI 0.70–0.94, $P < 0.001$, respectively).³⁹ The inter-observer intraclass correlation coefficient for the measurement of the β PPA area was 0.95 (95 % CI 0.90–0.98).

Thirty-seven eyes (52.1%) of 71 eyes with POAG patients had β PPA deep layer microvasculature dropout. The clinical and ocular characteristics of the POAG patients with and without dropouts were compared in Table 1. Eyes with microvasculature dropouts had a significantly higher prevalence of focal LC defects (70.3 vs. 32.4 %), lower cpVD (52.7 vs. 58.8 %), lower wiVD (43.7 vs. 48.7 %), worse VF MD (-9.06 vs. -3.83 dB), worse VF PSD (7.81 vs. 4.42 dB), thinner RNFL thickness (68.5 vs. 78.7 μ m), thinner total choroidal thickness (126.5 vs. 169.1 μ m), longer axial length (24.7 vs. 24.0 mm), larger β PPA area (1.2 vs. 0.76 mm²) and lower diastolic blood pressure (74.7 vs. 81.7 mmHg) than those without dropouts (all $P < 0.05$, respectively). Participants with microvasculature dropout were less likely to be African descent and tended to have higher systolic BP, but these differences did not reach statistical significance ($P = 0.075$ and $P = 0.091$, respectively). There was no significant difference between the two groups with respect to age, gender, spherical equivalent, CCT, presence of the diabetes and hypertension, antihypertensive and diabetes medication, glaucoma medications, IOP, MOPP, pulse rate, presence of the disc hemorrhage, and disc area (all $P > 0.10$).

The univariate and multivariable logistic regression analyses of the association between the presence of β PPA deep layer microvasculature dropout and clinical and ocular characteristics are presented in Table 2. Based on univariate logistic regression analysis, microvasculature dropout was significantly associated with longer axial length (odds ratio [OR], 1.49 ; $P = 0.036$), lower diastolic blood pressure (OR, 1.08; $P = 0.003$), lower wiVD (OR, 1.20; $P = 0.0001$), lower average cpVD (OR, 1.18; $P = 0.0001$), worse VF MD (OR, 1.18; $P = 0.0004$), worse VF PSD (OR, 1.29; $P = 0.0002$), thinner average cpRNFL thickness (OR, 1.09; $P = 0.0003$), higher prevalence of focal LC defects (OR, 4.94; $P = 0.001$), larger β PPA (OR, 4.47; $P = 0.002$), and thinner total choroidal thickness (OR, 1.02; $P = 0.0004$).

Presence of the DM (OR, 3.70; $P=0.098$) showed borderline significance. Age, race, gender, CCT, IOP, systolic BP, MOPP, prevalence of the hypertension and disc hemorrhage had no significant association with the presence of β PPA deep layer microvasculature dropout (all $P>0.16$). VF MD, VF PSD, average cpRNFL thickness, cpVD, and wiVD were significantly correlated ($P<0.001$, respectively), thus these five variables were separately included in the multivariate model to avoid multicollinearity. In the multivariate analysis with cpVD included, lower diastolic BP (OR, 1.16; $P=0.003$), higher prevalence of focal LC defect (OR, 6.27; $P=0.012$), thinner total choroidal thickness (OR, 1.02; $P=0.014$, respectively), and lower cpVD (OR, 1.27; $P=0.002$) remained as significant factors associated with the presence of β PPA deep layer microvasculature dropout. Similarly, in the multivariate analysis with VF MD included, lower diastolic BP (OR, 1.20; $P=0.002$), higher prevalence of focal LC defect (OR, 7.75; $P=0.012$), thinner total choroidal thickness (OR, 1.02; $P=0.012$), and worse VF MD (OR, 1.27; $P=0.001$) remained as significant factors (Table 2). Similar patterns were noted in the multivariate analysis with wiVD, VF PSD, and average cpRNFL thickness included, respectively; lower diastolic BP, higher prevalence of focal LC defects, thinner total choroidal thickness, and lower wiVD, worse VF PSD, and thinner average cpRNFL thickness, ($P<0.05$, respectively), remained as significant factors associated with the β PPA deep layer microvasculature dropout (Table 2).

Among the 37 eyes with the deep layer microvasculature dropout, 31 (83.8 %) eyes had dropout located in the infero-temporal (IT) sector, 13 eyes (35.1 %) in the supero-temporal (ST) sector, 12 eyes (32.4 %) in the temporal-upper sector, 9 eyes (24.3 %) in the temporal-lower sector, 2 eyes (5.4 %) in the inferonasal sector, and 1 eye (2.7 %) in the nasal-lower sector. Dropout was detected in only 1 sector in 23 eyes (62.2 %) and in 2 sectors in 14 eyes (37.8%).

All of the 26 eyes with both β PPA deep layer microvasculature dropout and focal LC defects showed topographic relationship between the two features. Microvasculature dropout was observed in the same sector as the largest focal LC defect in 24 eyes (92.3 %) and in the sector with the second largest focal LC defect in 2 eyes (7.7 %) (Fig 3).

Discussion

In the present study, dropout of the deep retinal layer microvasculature within the β PPA was well characterized using the choroidal layer vessel density map of optic nerve head OCT-A images. The presence of the focal LC defect, thinner RNFL thickness, worse VF MD and PSD, reduced RNFL vessel density, thinner choroidal thickness, and lower diastolic blood pressure were associated with the β PPA deep layer microvasculature dropout in POAG patients. These findings suggest that distinctive reduction of the parapapillary deep layer microvasculature may be involved in the pathophysiology of glaucomatous optic neuropathy. Specifically, β PPA deep layer microvasculature dropout may serve as a potential marker of the glaucoma severity, alteration of the lamina cribrosa morphology, and vascularity of the superficial retina.

In this study, the presence and location of focal LC defects were significantly and topographically related to β PPA deep layer microvasculature dropout in POAG patients.

Both LC defect and dropout were most commonly detected in the IT area followed by the ST area. Given that the microvasculature within the LC, deep retinal layers, and choroid share short posterior ciliary artery as a common source of perfusion,⁵⁻⁷ the β PPA deep layer microvasculature dropout may reflect disruption of the microvasculature contained within the laminar tissue. Such alternation of the laminar microvasculature may be related to the mechanical disruption of the laminar beams during the development of the focal LC defect.^{19, 20} Elucidation of the microvasculature within the ONH could be helpful for examining this hypothesis, however this is not possible with current OCT-A technology due to projection artifacts in which the superficial blood vessels project to deeper tissue.¹⁹

Reduced RNFL vessel density was another structural parameter that showed a significant association with the β PPA deep layer microvasculature dropout. The microvasculature within the superficial and deep retinal layers is perfused differently by the central retinal artery and short posterior ciliary artery, respectively.^{6, 7} Therefore, a mechanism that explains how the two vasculatures are related is unclear. One possible hypothesis is that disruption of the superficial microvasculature may be secondary to the axonal loss, while that of the deeper layer microvasculature is associated with the structural changes of deep ONH structures such as the LC. Second, LC morphology changes may lead to the impairment of the central retinal artery, as well as short posterior ciliary artery going through or beside the LC, and thus may lead to reduction of the parapapillary microvasculature within both choroid and superficial retina.⁴⁰ Third, the superficial and deeper retinal layer microvasculature may be directly related. Given that the deeper layer microvasculature dropout may be often accompanied by the β PPA which is devoid of the RPE, it is also possible that impaired blood-retinal layer barrier may facilitate the interaction between the deeper and superficial retinal microvasculature.^{3, 4, 38} In this study, β PPA area was significantly associated with the β PPA deep layer microvasculature dropout in a univariate analysis, but not in the multivariate analysis. These findings suggest that β PPA may be associated with peripapillary vascular disruption, but its influence may be relatively weak compared with other factors, such as focal LC defect, axonal loss, choroidal thickness, and superficial retinal microstructure. Particularly, β PPA area was associated with the total choroidal thickness ($R^2 = 0.087$, $P = 0.012$) (data not shown earlier), thus the association between the β PPA area and the deep layer microvasculature dropout may be masked in a multivariate analysis. To determine which, if any, of these speculative ideas are tenable, longitudinal studies on the relationship between the superficial and deep retinal layer microvasculature and axonal loss, focal LC defect and β PPA are needed.

β PPA deep layer microvasculature dropout was also related to more advanced glaucoma (worse MD and PSD and thinner cpRNFL thickness). These results are in line with previous reports that ICGA-derived hypofluorescence in the β PPA area is more commonly detected in glaucoma patients than in normal subjects.³ β PPA deep layer microvasculature dropout observed in this study can be interpreted as an independent risk factor for the development and progression of glaucoma or an epiphenomenon of other factors associated with the glaucoma severity such as LC changes or reduced microvasculature within the superficial retina. Prospective longitudinal studies on the temporal relationship between the deep layer microvasculature dropout and glaucoma progression may help elucidate this issue.

A thinner choroid was also significantly associated with the parapapillary deep layer microvasculature dropout in POAG patients. Histologically, deep retinal layer microvasculature within the β PPA is mainly comprised of the choriocapillaris.²⁵ Therefore, the current finding supports the notion that choroidal thinning may be associated with the loss of the choriocapillaris.²⁹

Interestingly, lower diastolic BP was significantly related to deep layer microvasculature dropout. Presence of systemic hypertension and number of the hypertensive medications did not differ between those with and without a dropout minimizing effect of the hypertensive medication. These findings are consistent with a study by Memarzadeh et al. that showed a significant association between lower diastolic BP and a higher prevalence of POAG, suggesting that reduced diastolic perfusion pressure may be involved in the pathophysiology of the glaucoma, at least in some patients.⁴¹

A number of studies suggested that increased mechanical stress on the ONH and parapapillary area during elongation of the eye globe may lead to a compromised parapapillary deep layer microvasculature in myopic eyes with thinner ocular wall.⁴²⁻⁴⁴ Disc hemorrhage, a vascular parameter associated with the presence and progression of the glaucoma,¹⁴ may also be associated with the dropout. However, in this study, disc hemorrhage was not found to be significantly associated with microvasculature dropout in both univariate and multivariate logistic regression. Longer axial length was marginally associated with the deep layer microvasculature dropout in a univariate logistic regression, but not in multivariate regressions. These results may be due in part to the relatively small number of eyes with high myopia (axial length ≥ 26.5 mm or spherical equivalent ≤ -6.0 diopter) ($n = 5$) and with disc hemorrhage ($n = 9$). It will be important to investigate the relationship of the deep layer microvasculature with these two parameters in a larger number of subjects with high myopia and disc hemorrhages.

The present study has several limitations. First, projection artifacts of the superficial vessels may lead to a false positive detection of vascularity within the deep retinal layers,⁹ and a dropout was defined as a complete loss of the microvasculature. Therefore, eyes with partially reduced microvasculature may have been classified as not having dropout. Qualitative determination of microvasculature dropout may be variable. However, these limitations were addressed at least in part by the excellent inter-observer agreement (Kappa = 0.86) for the presence of the dropout, and the ability to reach consensus in all but one eye. In addition, the fact that there are few superficial retinal vessels within the β PPA area reduced the potential effect of projection artifacts on our results. Further improvement of the OCT-A technique or the development of reliable post-processing software to reduce the projection artifacts of the superficial vessels to the deeper layers is needed. Second, this study has relatively small number of study subjects and did not enroll healthy normal controls. Since deeper layer microvasculature dropout may occur not only due to glaucoma, but also by other conditions affecting the ONH biomechanics, investigations on the non-glaucomatous eyes are warranted. Third, association between the deep layer microvasculature dropout and the microstructures of the β PPA (presence of the γ PPA which is devoid of the Bruch's membrane²⁵) was not evaluated in this study, since enhanced depth imaging SD-OCT was not available. Further investigation on this issue may elucidate the

vascular aspect of the β PPA microstructure in the development of and progression of the glaucomatous optic neuropathy.

In conclusion, the higher frequency of focal LC defects, more advanced glaucoma, reduced circumpapillary RNFL vessel density, thinner choroidal thickness, and lower diastolic blood pressure were significantly associated with the OCT-A-derived dropout of the deep retinal layer microvasculature within the β PPA in glaucomatous eyes. Longitudinal studies are needed to quantitatively assess the density of the deep layer microvasculature and to evaluate its temporal relationship with the glaucoma progression.

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Deep retinal layer microvasculature dropout assessed by optical coherence tomography angiography was associated with focal lamina cribrosa defect, more advanced disease status, reduced superficial microvasculature, thinner choroidal thickness, and lower diastolic blood pressure.

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Figure 1.

Analysis of the microvasculature within the deep retinal layer of the β -zone parapapillary atrophy (β PPA) using the choroidal layer vessel density map of optic nerve head optical coherence tomography (OCT) angiography images. Right images are the same as left images but annotated to indicate location of the horizontal B-scan (sky blue lines) and structural features analyzed. **A-1** and **A-2**, Boundaries of the optic disc (orange outlines and orange arrowheads) and β PPA (green outlines and green arrowheads) were delineated on the scanning laser ophthalmoscopy images (upper) and horizontal B-scan of the spectral domain-OCT (lower). **B-1** and **B-2**, Microvasculature within deep retinal layer of the β PPA (yellow outlines) was qualitatively evaluated on enface (upper) and horizontal (lower) B-scans of the choroidal vessel density maps. Note that deep retinal microvasculature located below the level of retinal pigment epithelium was well visualized without notable projection artifacts of the superficial retinal vessels within the β PPA area.

Figure 2.

Determination of the presence and location of the microvasculature dropout within the β -zone parapapillary atrophy (β PPA) deep retinal layer on the choroidal vessel density map of optic nerve head optical coherence tomography angiography images. **B** and **C** are the same as **A**, but annotated to indicate the location of the microvasculature dropout. Large blue arrows indicating the horizontal scan location. **A** and **B**: The deep layer microvasculature within the β PPA between the margin of the optic disc (orange outline) and β PPA (green outline) was assessed on the enface (**A-1** and **B-1**) and horizontal (**A-2** and **B-2**) B-scans of the choroidal vessel density maps. β PPA deep layer microvasculature dropout was defined as a complete loss of the vascularity below the level of the retinal pigment epithelium (yellow arrows). Note that reflectance (green arrows) or shadowing (red arrows) of the large vessels was excluded from the analysis of the microvasculature dropout. **C**: Deep layer microvasculature dropout was well demarcated on the enface choroidal vessel density map (yellow outline).

Figure 3.

Left eye of a primary open angle glaucoma patient with β -zone parapapillary atrophy (β PPA) deep layer microvasculature dropout on the choroidal vessel density map of the optic nerve head optical coherence tomography (OCT) angiography scan. The patient has a diastolic blood pressure of 79 mmHg and total choroidal thickness of 93 μ m. **A** and **B**: RNFL defects (outside normal limits identified in red) in the inferotemporal (IT) and inferonasal (IN) sectors (black arrowheads) were noted on the spectral-domain OCT (**A**). RNFL defects were compatible with superior visual field scotomas observed in the pattern standard deviation plots of the standard automated perimetry (**B**). **C** and **D**: Enface (**C**) and horizontal (**D**) B-scans of the swept source (SS)-OCT. **C-2** and **D-2** are the same images as **C-1** and **D-1** but are labeled to indicate the horizontal scan location (large blue arrows) through the focal lamina cribrosa (LC) defect. A focal LC defect was located mainly in the IT sector (red arrows) (**C-2** and **D-2**). **E**: Vessel density map of the RNFL (**E-1**), and the same image including a 8-sector circle with vessel density values for each sector (**E-2**). Notable vessel density reduction in the corresponding IT and IN sectors (black outlined red arrowheads) was observed. **F** and **G**: Enface (**F-1**, **F-2**, and **F-3**) and horizontal (**G-1** and **G-2**) B-scans of choroidal layer vessel density maps. **F-2** and **F-3** are same as **F-1**, and **G-2** same as **G-1**. **F-2** and **G-2** contain large blue arrows indicating the location of the horizontal

B-scan. Well delineated deep layer microvasculature dropout (yellow outlines) within the β PPA (green outlines) (**F-2** and **G-2**) were observed mainly in the IT sector (**F-3**).

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Table 1

Comparison of the demographics and test results between primary open angle glaucoma patients with and without the deep retinal layer microvasculature dropout within the β PPA.

Variables	Eyes with microvascular dropout (37 eyes, 37 patients)	Eyes without microvascular dropout (34 eyes, 34 patients)	p-value
Age (years)	73.6 $\pm$ 12.8 (36.7 to 94.5)	72.7 $\pm$ 9.4 (51.5 to 87.0)	0.754 [*]
Gender (male/female)	19/18	15/19	0.710 [†]
Spherical equivalent (D)	-1.7 $\pm$ 2.4 (-8.4 to 1.3)	-1.0 $\pm$ 2.0 (-5.8 to 2.1)	0.210 [*]
Axial length (mm)	24.7 $\pm$ 1.6 (22.4 to 29.0)	24.0 $\pm$ 0.97 (21.8 to 26.1)	0.041 [*]
CCT (μ m)	523.7 $\pm$ 42.4 (425.3 to 606.0)	534.0 $\pm$ 39.9 (450.7 to 623.7)	0.298 [*]
Ethnicity (Asian/European/African descent)	6/27/4	3/20/11	0.075 [†]
Self-reported history of diabetes, n (%)	2 (5.4 %)	6 (17.6 %)	0.201 [†]
Self-reported history of hypertension, n (%)	20 (54.1 %)	16 (47.1 %)	0.725 [†]
Antihypertensive medication, n (%)	17 (45.9 %)	14 (41.2 %)	0.869 [†]
Diabetes medication, n (%)	1 (2.7 %)	5 (14.7 %)	0.165 [†]
Number of topical glaucoma medications			0.262 [†]
0	9	8	
1	11	16	
>1	17	10	
Topical medications, n			
Prostaglandin analogues	23	22	0.796 [†]
Beta-antagonists	10	8	
Carbonic anhydrase inhibitors	12	8	
IOP (mmHg)	13.4 $\pm$ 5.0 (5.0 to 24.0)	15.1 $\pm$ 4.9 (5.0 to 30.0)	0.179 [‡]
Systolic BP (mmHg)	127.4 $\pm$ 14.8 (92.0 to 153.0)	123.5 $\pm$ 12.9 (102.0 to 162.0)	0.091 [‡]
Diastolic BP (mmHg)	74.7 $\pm$ 9.0 (51.0 to 93.0)	81.7 $\pm$ 10.3 (65.0 to 104.0)	0.003 [*]
Mean ocular perfusion pressure (mmHg)	53.0 $\pm$ 7.3 (36.2 to 65.6)	54.7 $\pm$ 8.0 (42.9 to 75.8)	0.385 [*]
Pulse rate (bpm)	65.8 $\pm$ 12.0 (44.0 to 108.0)	68.2 $\pm$ 11.9 (46.0 to 96.0)	0.407 [*]
Disc Hemorrhage, n (%)	4 (10.8 %)	5 (14.7 %)	0.892 [†]
Visual field MD (dB)	-9.06 $\pm$ 6.71 (-29.05 to -1.72)	-3.83 $\pm$ 5.67 (-25.87 to 2.40)	< 0.0001 [‡]
Visual field PSD (dB)	7.81 $\pm$ 3.77 (1.63 to 14.57)	4.42 $\pm$ 3.38 (1.49 to 14.28)	0.0001 [‡]
Disc area (mm ²)	2.1 $\pm$ 0.4 (1.2 to 3.0)	2.0 $\pm$ 0.5 (0.9 to 3.0)	0.477 [*]
Average cpRNFL thickness (μ m)	68.5 $\pm$ 11.1 (41.5 to 98.9)	78.7 $\pm$ 12.1 (51.0 to 110.7)	0.0004 [*]
Average cpVD (%)	52.7 $\pm$ 6.6 (38.1 to 62.5)	58.8 $\pm$ 5.7 (48.1 to 71.5)	0.0001 [*]
Average wiVD (%)	43.7 $\pm$ 5.2 (30.2 to 53.3)	48.7 $\pm$ 5.4 (37.2 to 60.8)	0.0001 [*]
Focal lamina cribrosa defect, n (%)	26 (70.3 %)	11 (32.4 %)	0.0031 [‡]
β PPA area (mm ²)	1.2 $\pm$ 0.12 (0.24 to 3.49)	0.76 $\pm$ 0.37 (0.18 to 1.78)	0.0076 [‡]
Total choroidal thickness (μ m)	126.5 $\pm$ 42.8 (67.5 to 243.5)	169.1 $\pm$ 55.0 (87.5 to 277.0)	0.0007 [‡]

Continuous variables are shown in mean $\pm$ standard deviation (range).
Statistically significant values are shown in bold.

*The comparison was performed by using independent samples t-test.

[†]The comparison was performed by using Chi-squared test.

[‡]The comparison was performed by using Mann-Whitney test.

CCT = central corneal thickness; IOP = intraocular pressure; BP = blood pressure; MD = mean deviation; PSD = pattern standard deviation;
cpRNFL = circumpapillary retinal nerve fiber layer; cpVD = circumpapillary vessel density; wiVD = whole image vessel density; β PPA = β -zone
parapapillary atrophy.

Table 2

Logistic regression testing factors associated presence of the deep retinal layer microvascular dropout within the β PPA ($n = 71$).

Variables	Univariate Model		Multivariate Model 1* with cpVD included		Multivariate Model 2* with VF MD included		Multivariate Model 3* with cpRNFL thickness included	
	Odds ratio, 95 % CI	P value	Odds ratio, 95 % CI	P value	Odds ratio, 95 % CI	P value	Odds ratio, 95 % CI	P value
Age, per 1 yr older	1.01, 0.97–1.05	0.750						
Female sex (vs. male)	1.34, 0.53–3.40	0.542						
White race (vs. non-white)	1.87, 0.70–4.96	0.208						
CCT, per 1 μ m thinner	1.01, 0.99–1.02	0.290						
Axial length, per 1mm longer	1.49, 1.00–2.23	0.036						
IOP, per 1mmHg lower	1.08, 0.97–1.18	0.165						
Systolic BP, per 1mmHg higher	1.02, 0.99–1.06	0.240						
Diastolic BP, per 1mmHg lower	1.08, 1.02–1.14	0.003	1.16, 1.05–1.28	0.003	1.20, 1.06–1.35	0.002	1.14, 1.04–1.25	0.005
Mean ocular perfusion pressure, per 1mmHg lower	1.03, 0.97–1.10	0.376						
Diabetes, presence	3.70, 0.70–20.0	0.098						
Hypertension, presence	1.32, 0.52–3.33	0.556						
Disc hemorrhage, presence	1.42, 0.35–5.88	0.622						
cpVD, per 1% lower	1.18, 1.08–1.30	0.0001	1.27, 1.09–1.49	0.002				
Visual field MD, per 1 dB worse	1.18, 1.05–1.32	0.0004			1.27, 1.10–1.45	0.001		
Average cpRNFL thickness, per 1 μ m thinner	1.09, 1.03–1.14	0.0003					1.10, 1.03–1.18	0.008
Focal lamina cribrosa defect, presence	4.94, 1.80–13.5	0.001	6.27, 1.50–26.19	0.012	7.75, 1.56–38.48	0.012	5.78, 1.44–23.22	0.014
β PPA area, per 1 mm ² increase	4.47, 1.44–13.91	0.002						
Total choroidal thickness, per 1 μ m thinner	1.02, 1.01–1.03	0.0004	1.02, 1.00–1.08	0.014	1.02, 1.00–1.08	0.012	1.02, 1.00–1.08	0.021

Statistically significant values are shown in bold.

* Adjusted for all variable with P of < 0.1 in univariate regression model

CI = confidence interval; CCT = central corneal thickness; IOP = intraocular pressure; BP = blood pressure; MD = mean deviation; cpRNFL = circumpapillary retinal nerve fiber layer; cpVD = circumpapillary vessel density; β PPA = β -zone parapapillary atrophy.