Ocular Determinants of Peripapillary Vessel Density in Healthy African Americans: The African American Eye Disease Study

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PURPOSE. The African American (AA) population has unique ocular anatomic characteristics and a disproportionately high incidence of glaucoma, which is associated with lower peripapillary vessel density (VD). This study aimed to identify ocular determinants of peripapillary VD in healthy AAs.

METHODS. This was a cross-sectional, population-based study of 1029 AAs, ages 40 and older. Participants underwent examination to obtain axial length (AL), IOP, central corneal thickness (CCT), mean retinal nerve fiber layer (RNFL) thickness, visual field mean deviation (MD), and 6×6-mm optical coherence tomography angiography scans of the optic nerve. Participants with glaucoma, vision-threatening diabetic retinopathy, or other relevant ocular disease were excluded. Prototype software was used to quantify VD. A multivariable regression model, controlling for age and signal strength, identified the ocular variables that predicted peripapillary VD. The contribution of each variable was assessed with the magnitude of standardized regression coefficients (SRC).

RESULTS. Based on univariate regressions, AL, RNFL thickness, and MD had significant associations with peripapillary VD (all $P < 0.001$). In the final multivariate model, lower mean RNFL thickness ($\beta = 0.0022$, $P < 0.001$, SRC = 0.542) and longer AL ($\beta = -0.0055$, $P < 0.001$, SRC = −0.118) were associated with lower peripapillary VD, controlling for age and signal strength, with model R^2 of 0.69.

CONCLUSIONS. Thinner RNFL and longer AL were the most influential ocular determinants of lower peripapillary perfusion in healthy AA eyes. Additional research is needed to clarify whether longer AL increases risk of glaucoma by affecting capillary perfusion.

Keywords: optical coherence tomography angiography, glaucoma, retinal blood flow, epidemiology

The prevalence of glaucoma in African Americans (AA) ranges from 4% in ages 50 to 59 to 13% in ages 80 to 89, much greater than the 2% to 3% prevalence in Americans overall.[1] In fact, glaucoma is currently the leading cause of irreversible blindness in AA in the United States.[2] Interestingly, Siesky et al.[3] found reduced retrobulbar blood flow in AA eyes compared with those of European descent with similar IOP and glaucoma staging. AAs on the whole have been shown to have differences in other ocular anatomic characteristics, including thinner central corneal thickness (CCT),[4,5] larger optic nerve head (ONH),[6] increased cup-to-disc ratio (CDR),[7] more beta zone peripapillary atrophy,[8] and reduced pattern standard deviation on automated perimetry visual fields,[4] as compared with Caucasian populations. The degree to which such differences in ocular anatomic characteristics may contribute to the higher rates of glaucoma in AA deserves exploration.

Optical coherence tomography angiography (OCTA) is a noninvasive imaging technique, which provides high-resolution imaging of the retinal microvasculature with high repeatability and reproducibility.[9] OCTA can be used to quantify vascular perfusion of the radial peripapillary capillaries (RPC) plexus that supplies the RNFL, and reduced peripapillary vessel density (VD) has been shown to be a good diagnostic marker of glaucoma.[10-12] Currently, little is known regarding the ocular variables that may influence peripapillary VD in healthy subjects.[13-15] These data are important as clinicians and scientists seek to understand the utility of peripapillary VD measurements for glaucoma and other conditions in patients

with varying ocular anatomy. In this study, we sought to identify ocular anatomic factors associated with lower peripapillary VD in healthy AA eyes. We hypothesized that risk factors for glaucoma, such as elevated IOP, thin CCT, and myopia may be associated with lower peripapillary VD, which could then support a mechanistic link between these risk factors and subsequent glaucomatous optic neuropathy.

METHODS

This study was approved by the Health Science Institutional Review Board of the University of Southern California, is compliant with the Health Insurance Portability and Accountability Act of 1996 and is adherent to the tenets of the Declaration of Helsinki.

Study Population

In this population-based, cross-sectional study, AA aged 40 years and older living within 30 Census tracts in and around Inglewood, California, were invited to participate over a 5-year period from January 2013 through December 2017. Of the target population, approximately 8000 subjects, over 6300 AA participated in the study upon completion, resulting in a participation rate of approximately 80%. The study design and data collection methods have been previously published.[16] In short, during household screening, interviewers explained the study, obtained informed consent, and conducted an in-home, computer-assisted interview. OCTA scans were introduced in the study beginning in February 2016, and subjects who received OCTA imaging were potential participants in this study.

Clinical Assessment

Study participants visited a local eye examination center for a comprehensive examination by one ophthalmologist and several technicians. Participants first completed an in-clinic questionnaire to determine medical and ocular history, potential risk factors for ocular disease, and access to healthcare before proceeding to the eye examination. At the conclusion of the visit, the ophthalmologist discussed results with the participants, made appropriate diagnoses, and provided referrals for specialty care if needed. Healthy participants included normal and glaucoma suspects based on the presence of a nonglaucomatous optic disc. Glaucoma diagnosis was made by the comprehensive ophthalmologist and was based on clinical examination, including evaluation for an optic nerve rim defect characteristic of glaucoma and visual field assessment. Participants were excluded for the following reasons: diagnosis of glaucoma or vision-threatening diabetic ocular disease (including severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular edema); signal strength (SS) less than seven (of 10); and poor image quality as assessed by a standardized image-quality grading algorithm. For subjects with both eyes meeting inclusion criteria, the right eye was selected for analysis to prevent bias due to intereye correlation.

Measurement of Ocular Variables

IOP was measured three times before pupil dilation with Goldmann applanation tonometry, and these values were averaged for each eye. Blood pressure was measured twice and averaged. Mean RNFL thickness measurements were obtained from OCT (Cirrus 5000 HD-OCT; Carl Zeiss Meditec, Dublin, CA, USA). CCT and axial length (AL) measurements were obtained from A-scan ultrasound and recorded as the average of 3 measurements (4000B A-Scan/Pachymeter; DGH Technology, Inc., Exton, PA, USA). Global mean deviation (MD) was recorded using the Humphrey Field Analyzer II Swedish Interactive Threshold Algorithm 24-2 (Carl Zeiss Meditec). Participants also underwent 6 × 6-mm optic nerve head scan using spectral domain-OCTA (Cirrus 5000 HD-OCT with Angioplex; Carl Zeiss Meditec). A single ONH scan was done for each eye of each participant.

Vessel Density Quantification

Two-dimensional en face OCT angiograms of the RPC layer were generated with automated segmentation software (Cirrus 11.0), with the RPC defined as the segment extending superficially from the inner limiting membrane to the posterior surface of the RNFL. En face images were then processed using custom software with an interactive interface in order to quantify the RPC vascular density using a previously described method.[17] The software used a method combining a global threshold, Hessian filter, and adaptive threshold to generate binary vessel maps, which were used to calculate quantitative indices of blood flow in MATLAB (R2017a; MathWorks, Inc., Natick, MA, USA). The avascular zone of the ONH was manually selected to establish baseline background noise level for global thresholding, and the ONH was excluded from quantification. Large vessels greater than 32 μm in diameter were also excluded. VD was defined as the unitless ratio of the total image area occupied by white pixels in the binary vessel map to the total image area of all pixels.

Statistical Analysis

The ocular variables that we assessed were AL, CCT, IOP, RNFL thickness, and MD. Mean and standard deviation were calculated for each of the ocular variables, as well as for age and OCTA SS. Univariate linear regressions were performed for each pair of variables with peripapillary VD as well as with each other. A preliminary analysis of the relationship between mean arterial pressure and peripapillary VD was also performed, and no significant association was found.

We used multivariable linear regression models to assess the contributions of AL, CCT, IOP, visual field MD, and mean RNFL thickness to the dependent variable, peripapillary VD. The best-fit model was chosen using stepwise selection with cut-off point of $P = 0.05$. The relative contribution of each independent variable to the VD was assessed using the magnitude of standardized regression coefficients (SRC). Variance inflation coefficients were computed to assess for collinearity in the multivariable model. The model R^2 reflects the proportion of variation in peripapillary VD that is explained by the ocular variables in the model, along with age and SS. Locally weighted scatterplot smoothing (LOWESS) plots were generated to reflect the relationship between peripapillary VD and the ocular variables included in the multivariable model.[18] LOWESS regression lines used localized smoothing, such that the relative strength of associations at different variable values can be visually appreciated. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

We also performed the same univariate regressions and multivariable model selection procedure using peripapillary flux, defined as the average flow intensity within the detected vasculature in the binary vessel map, rather than VD to assess whether there was a difference between the two parameters. We have previously reported that the diagnostic accuracy of flux in glaucoma is comparable to that of VD.[19,20] Analysis revealed no significant differences between determinants of peripapillary flux versus VD. Given that VD is the more commonly used parameter in OCTA analysis, we chose to focus on the determinants of VD rather than flux.
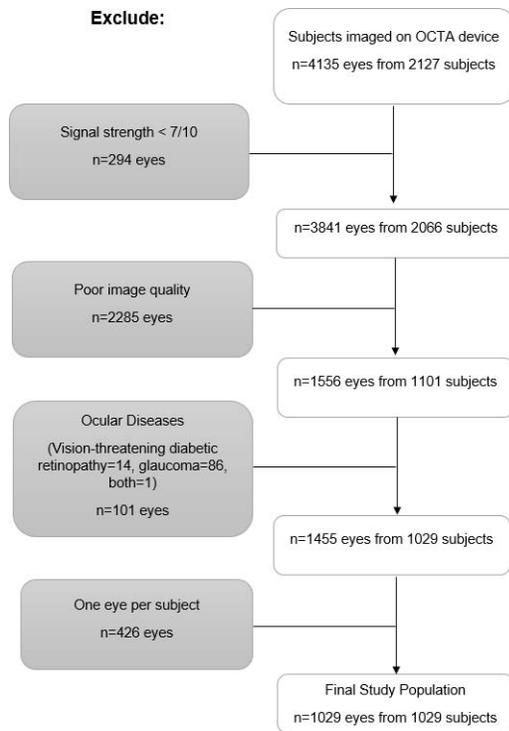
Exclude:

Subjects imaged on OCTA device
n=4135 eyes from 2127 subjects

Signal strength < 7/10
n=294 eyes

n=3841 eyes from 2066 subjects

Poor image quality
n=2285 eyes

n=1556 eyes from 1101 subjects

Ocular Diseases
(Vision-threatening diabetic retinopathy=14, glaucoma=86, both=1)
n=101 eyes

n=1455 eyes from 1029 subjects

One eye per subject
n=426 eyes

Final Study Population
n=1029 eyes from 1029 subjects

FIGURE 1. Flow chart of inclusion and exclusion criteria for imaged subjects.

RESULTS

Study Cohort

Of 2127 subjects, 4135 eyes received OCTA imaging. Two hundred ninety-four images were excluded due to SS less than 7 of 10. Because of poor image quality, 2285 images were excluded. Because of the presence of preexisting ocular disease, 101 images were excluded, of which 14 were due to vision-threatening diabetic retinopathy, 86 due to glaucoma, and 1 due to both (Fig. 1). The right eye scan was selected for the remaining subjects with imaging of both eyes, resulting in the further exclusion of 426 images. From 1029 subjects, 1029 eyes were analyzed. One hundred ninety-eight diabetic subjects were included in the analysis, 48 of whom had mild or moderate nonproliferative diabetic retinopathy. Excluded subjects had greater age (62 ± 11, $P < 0.001$), greater AL (23.75 ± 1.16, $P < 0.001$), poorer best-corrected visual acuity (24.71 ± 53.06 vs. 18.43 ± 5.33, $P < 0.001$), and greater MD (-2.50 ± 4.75, $P < 0.001$) than included subjects, with no significant difference in sex (63.7% vs. 64.1% female, $P = 0.792$), IOP (15.29 ± 3.61 vs. 15.19 ± 3.01, $P = 0.184$), or CCT (532.59 ± 36.57 vs. 532.54 ± 34.98, $P = 0.485$). Preliminary analysis revealed no significant association between image quality scores and peripapillary VD or ocular characteristics. Of the 1029 eyes analyzed, 369 (36%) were male and mean age was 58 (± 10) years.

Ocular Variables

Table 1 presents the mean and standard deviation for each of the ocular variables as well as age and SS,[21,22] and the results of the univariate linear regression of each variable with VD as the dependent variable. In univariate analysis, the factors significantly correlated with lower peripapillary VD were older age ($\beta = -0.0017$ per year, $P < 0.001$), decreased SS ($\beta = 0.029$, $P <$

TABLE 1. Distribution of Ocular Variables and Univariate Linear Regressions With Peripapillary Vessel Density in Healthy African Americans

Variable	N	Mean*	Beta†	P Value†
VD	1029	0.346 ± 0.045	–	–
Age, y	1029	57.93 ± 9.89	-0.00170	<0.001
SS	1029	9.26 ± 0.84	0.0291	<0.001
IOP, mm Hg	1002	15.19 ± 3.01	-7.997×10^{-4}	0.090
CCT, μm	1001	532.5 ± 35.0	4.542×10^{-5}	0.264
AL, mm	1000	23.57 ± 0.97	-0.01439	<0.001
Mean RNFL thickness, μm	1021	91.97 ± 10.80	0.00270	<0.001
Visual field MD, dB	983	-1.11 ± 3.22	0.00177	<0.001

* Mean values are depicted as mean ± SD.
† Beta coefficients and P values calculated from univariate linear regression with vessel density.

0.001), longer AL ($\beta = -0.014$ per mm, $P < 0.001$), thinner mean RNFL thickness ($\beta = 0.0027$ per μm, $P < 0.001$), and more negative MD ($\beta = 0.0018$ per dB, $P < 0.001$). IOP ($P = 0.090$) and CCT ($P = 0.264$) were not significantly associated with VD.

Determinants of Peripapillary Vessel Density

The final multivariable model included AL and mean RNFL thickness, controlling for age and SS (Table 2).[21,22] These four factors accounted for 69% of the variation in peripapillary VD (R^2). Thinner RNFL ($\beta = 0.0022$ per μm, $P < 0.001$, SRC = 0.543) and longer AL ($\beta = -0.0055$ per mm, $P < 0.001$, SRC = -0.117), were associated with lower peripapillary VD, respectively. Age ($\beta = -0.00088$ per year, $P < 0.001$, SRC = -0.196) and SS ($\beta = 0.021$, $P < 0.001$, SRC = 0.402) were also associated with lower peripapillary VD. The univariate association with peripapillary VD for MD was no longer significant in the multivariable model. Figure 2 presents the predicted values for peripapillary VD plotted against RNFL thickness in clustered 10-μm intervals with LOWESS regression lines and 95% confidence intervals. A reduction in peripapillary VD is seen with thinner RNFL. Figure 3 presents the same information for AL in 0.5-mm intervals, where a reduction in peripapillary VD is seen with increased AL.
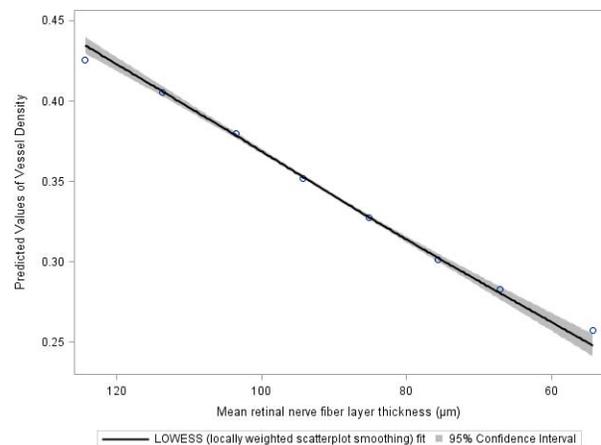

FIGURE 2. Predicted values of peripapillary VD versus mean RNFL thickness in healthy AA. The LOWESS plot is from a multivariable model controlling for age, SS, and AL. Plotted data points represent the average predicted VD values for each 10-μm thickness interval.
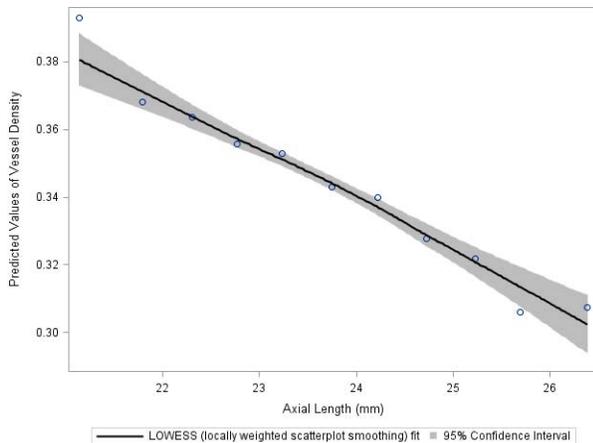
FIGURE 3. Predicted values of peripapillary VD versus AL in healthy AA. The LOWESS plot is from a multivariable model controlling for age, SS, and RNFL thickness. Plotted data points represent the average predicted VD values for each 0.5-mm AL interval.

DISCUSSION

To our knowledge, the African American Eye Disease Study is not only the largest but also the only population-based OCTA study to date. In this study of AA eyes without pre-existing disease, we evaluated the ocular determinants of peripapillary VD, a measure now being used as a marker for glaucoma disease. We found that, controlling for age and SS,[21,22] longer AL and thinner RNFL predicted lower peripapillary VD. This population-based study underscores the importance of understanding the influence of ocular anatomical variation on peripapillary perfusion measurements and also offers a potential pathophysiologic explanation for axial elongation increasing risk for glaucoma.

Strong, positive associations between RNFL thickness and peripapillary VD have been previously reported,[23,24] and support the idea that, in general, the quantity of perfused RPCs is proportional to the quantity of RNFL it is supplying.[25–27] Prior histology and OCTA studies have demonstrated how RPCs run parallel to the RNFL and that their densities within a given eye are highly correlated.[26,28] The current epidemiologic findings suggest that persons with greater RNFL thickness also have greater density of the RPCs. While we do not know if baseline peripapillary VD indicates future risk for glaucoma, there is some evidence that thin mean RNFL is a risk factor for the progression of visual field loss in glaucomatous eyes, as well as for the development of visual field deficits in glaucoma suspect eyes.[29–33] There are currently no longitudinal data to determine whether peripapillary VD is a risk factor for functional progression of glaucoma. Given the strong, positive correlation between VD and RNFL thickness, this deserves further exploration in longitudinal studies.

While RNFL thickness has been established as a good clinical marker for glaucoma and its progression,[34] the strong relationship between RNFL thickness and peripapillary VD supports the newer findings that peripapillary VD is also a good clinical marker for glaucoma.[19,20,35–37] However, what remains unclear is the temporal relationship between RNFL thinning and peripapillary VD reduction in glaucoma, or at least certain instances of glaucoma. It may be that thinning of the RNFL reduces metabolic demand for the RPCs. Alternatively, in at least some instances of glaucoma, vascular dysregulation and unstable ocular blood flow may lead to reperfusion injury, damage to the retinal ganglion cell axons, and resultant RNFL thinning.[38] Elucidating this temporal relationship is essential to better understanding the pathogenesis of glaucomatous optic neuropathy.

Greater AL was the other ocular factor associated with lower peripapillary VD in our population, and this finding may provide insight into glaucoma pathogenesis. To date, the negative correlation between AL and peripapillary VD has only been demonstrated in small studies of young myopic patients in China.[15,23,39] These findings are consistent with previous reports, which used fluorescein angiography to detect reduced retinal perfusion in myopic eyes.[40] Healthy myopic eyes have less retrobulbar blood flow associated with decreased peak flow velocity in the central retinal artery,[41] smaller vessel diameter,[42,43] and increased flow resistance.[44] A current hypothesis is that AL elongation causes these changes through mechanical stretching and thinning of the choroid, retina, and its vasculature.[45] Alternatively, the mechanical thinning of the choroid leading to reduced oxygen delivery to the retina may cause secondary retinal vasoconstriction and reduction in microcirculation.[45] A significant association between AL elongation and RNFL thinning has been shown in prior studies.[46,47] However, our study demonstrates that despite the relationship between AL and RNFL thickness, there is an independent relationship between AL and VD, which is not explained by RNFL thinning. If the lower retinal perfusion in longer eyes were due to RNFL thinning alone, we would not expect AL to maintain its independent association with peripapillary VD in the multivariable model. One possible explanation is that axial elongation causes lower VD not only from RNFL thinning leading to a proportionally reduced need of RPCs, but also because there is a primary mechanical stretching of the retinal vasculature itself. In fact, it is possible this may indicate why greater AL is a risk factor for glaucoma. If longer eyes have lower peripapillary blood flow, they may be more susceptible to glaucomatous damage from IOP elevation or vascular factors. Further reduction in capillary blood flow within the lamina cribrosa and peripapillary area could diminish the diffusion of nutrients to adjacent astrocytes and retinal ganglion axons, leading to glaucomatous progression.[48–51] The findings of this study provide preliminary support for this idea, but longitudinal studies are needed to further explore this hypothesis.

An alternate explanation is that the association between axial elongation and lower peripapillary VD is a product of magnification error in the OCTA device.[52] Longer eyes have larger scanning circle diameters, such that the area of vasculature that is quantified is actually larger than anticipated and the VD is lower as a result. However, magnification error would not account for the reduced ocular and retrobulbar blood flow observed in myopia in other studies, as they used modalities, such as laser doppler flowmetry and color doppler imaging, which would not be susceptible to magnification error.[41–45]

Notably, we observed in our population that increasingly negative MD was significantly associated with lower peripapillary VD in univariate regressions but was no longer a significant association in the multivariable model. We did not observe R^2 values greater than 0.5 for MD with any other variable in the univariate regressions, nor did we observe a

TABLE 2. Multivariable Model* of Ocular Determinants of Radial Peripapillary Capillary Vessel Density in African Americans Without Pre-Existing Ocular Disease

Variable	Parameter Estimates (95% CI)	SRC†	P Value
Mean RNFL thickness, μm	0.0022 (0.0021, 0.0024)	0.542	<0.001
AL, mm	−0.0055 (−0.0070, −0.0035)	−0.118	<0.001

* Model controlled for SS and age. Model R^2 was 0.69.
† SRC, standardized regression coefficient.

significant value for the respective variance inflation factor (VIF) when included in the multivariable model, indicating that MD is not collinear with any other variable. Our data therefore suggest that any relationship between MD and peripapillary VD is better explained by the other factors in the final model. It is also possible that an independent contribution of MD to peripapillary VD could potentially be identified with a larger study population.

Our study controlled for age and SS in all analyses, as suggested by prior findings,[21,22] and the significant association of these factors with peripapillary VD in our study supported the importance of doing so. Significant reduction in peripapillary VD has been reported in healthy eyes above age 60[21] and a linear relationship between age and VD has also been reported in the macula in younger populations.[13] We found that increasing age was associated with reduction of peripapillary VD, and age was a more significant predictor of peripapillary VD than was AL in our model. Further, we found that reduction in SS is associated with lower peripapillary VD. Most OCTA studies use a SS of six or seven as minimal inclusion criteria, as the manufacturer recommends SS of six or more to indicate adequate quality.[53] However, Lim et al.[22] reported significant differences in macular VD when comparing images with SS from seven to nine, with no significant difference between SS nine and ten. Decreased SS causes attenuation of all signals, such that the device is less likely to detect blood flow signals in small vessels against the background noise threshold.[54] Our data support the recent findings that VD measurement is affected by SS even when using seven as the minimum inclusion criteria. Consequently, SS should be taken into account when analyzing OCTA images, especially when comparing images of differing SS. Further studies should be performed to determine the optimal minimum SS inclusion criteria for analysis in the peripapillary region.

An important limitation of our study is that we had to exclude a significant number of participants due to poor image quality. This was done to limit the variability in VD quantification from outside variables, such as artifacts, segmentation errors, and media opacities, but this may have led to some bias in our results. Second, our study consisted of participants who identified themselves as AA, but ancestry markers were not assessed. Future studies using ancestry markers would allow for a more well-defined study population.

In summary, this study demonstrates that thin RNFL and increased AL are independent ocular anatomic predictors of lower peripapillary VD in healthy AA eyes. Ocular anatomic variation should be considered when assessing peripapillary VD, and future research should further explore whether axial elongation increases risk for glaucoma by affecting the microcirculation supplying retinal ganglion axons.

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APPENDIX

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