The Deep Vascular Plexus Density Is Closely Related to Myopic Severity

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\textbf{Keywords}
Retinal microvasculature · Deep vascular plexus · Myopia · Optical coherence tomography angiography

\section*{Abstract}
\textbf{Objectives:} The aim of the study was to investigate the relationship between myopic severity and the retinal microvasculature based on quantitative variables using optical coherence tomography angiography (OCTA) and to identify OCTA indicators of microvascular network loss in myopia. \textbf{Methods:} This cross-sectional study included 123 eyes of 123 myopic subjects. The included eyes were divided into three groups according to the spherical equivalent (SE) and axial length (AL): low myopia (LM) (−3.00 D ≤ SE ≤ −0.50 D), moderate myopia (MM) (−6.00 D ≤ SE < −3.00 D), and high myopia (HM) (−9.00 D ≤ SE < −6.00 D or AL > 26 mm). All the eyes underwent OCTA scans. The densities and thicknesses of the macular and peripapillary zones, including the foveal avascular zone (FAZ) area, superficial vascular plexus (SVP) density, deep vascular plexus (DVP) density, ganglion cell complex (GCC) thickness, full retinal thickness, radial peripapillary capillary plexus (RPCP) density, and retinal nerve fiber layer (RNFL) thickness, were automatically exported. \textbf{Results:} Compared to the LM or MM group, the HM group had a significantly reduced FAZ area (\(p < 0.05\)). In most sectors of the parafoveal and perifoveal areas, the HM group had significantly lower DVP density and higher retinal thickness than the LM and MM groups (all \(p < 0.05\)). However, significant differences among the three groups in only one or several sectors were observed with regard to SVP density, GCC thickness, and RNFL thickness, and no significant differences among the three groups in any sector were noticed in RPCP density. Perifoveal DVP density and perifoveal full retinal thickness were positively associated with SE and negatively associated with AL in stepwise multiple linear regression analyses adjusted for sex and age. \textbf{Conclusion:} DVP density was closely related to myopic severity. Reduced perifoveal DVP density may serve as an indicator of microvascular network loss in myopia. OCTA may provide useful and crucial information for monitoring the progression of myopia.

\section*{Introduction}
Myopia is a blurred vision condition in which the images of objects focus in front of the retina because of axial elongation of the eyeball \cite{1}. Myopia is one of the most common causes of correctable visual impairment in young adults, especially in Southeast Asia \cite{2}. It is estimated that 5 billion people globally will have myopia by 2050 \cite{3}. The increasing prevalence of myopia urges us to control its progression because high myopia (HM) may...
result in many severe ocular complications, such as retinal detachment and macular neovascularization, which can in turn dramatically affect visual function. Previous studies have revealed that alterations in retinal microvasculature may be related to the development and progression of myopia and its complications [4]. However, imaging modalities may contribute to discrepancies. Different imaging methodologies have been adopted to identify the indicators of microvascular alterations, but the results are varied and ambiguous. There is no uniform standard in microvascular assessment. Fundus photographs and fundus fluorescein angiography, which are frequently applied to evaluate retinal microvasculature, are not quantitative methods [5, 6]. Therefore, the microvascular conditions and their accurate relationship with the severity of myopia cannot be determined. Moreover, fundus fluorescein angiography is an invasive examination that requires intravenous dye injection and may cause severe anaphylactic reactions [7].

In the past few years, a noninvasive cross-sectional real-time imaging device, optical coherence tomography (OCT) angiography (OCTA), has been introduced, which provides microvascular network details of different retinal layers for clinical diagnosis [8]. OCTA offers results with high repeatability and reproducibility [9, 10]. Nevertheless, different imaging analysis methods have been used in previous studies, which may also contribute to the discrepancies [11, 12]. Currently, the number of studies assessing the retinal microvasculature of myopic eyes using OCTA is relatively small, and the conclusions are inconsistent [13, 14]. In addition, the peripapillary zone has seldom been evaluated in previous studies, while both the macular zone and the peripapillary area were analyzed in our study. As such, the purpose of this study was to investigate the relationship between myopic severity and retinal microvasculature based on quantitative variables using OCTA and to identify OCTA indicators for loss of microvascular network in myopia.

**Methods**

**Subjects**

This was a cross-sectional study approved by the Ethics Committee of Ningbo Eye Hospital (approval number: 2019-QTKY-21). It was conducted in compliance with the tenets of the Declaration of Helsinki. Consecutive patients' medical records obtained between July 2020 and June 2021 in the ophthalmology outpatient department were reviewed. All individuals underwent complete ophthalmic examinations, including best-corrected visual acuity (BCVA), objective (KR-8900; Topcon, Tokyo, Japan) and subjective optometry, intraocular pressure (TX-20; Canon Inc., Tokyo, Japan), axial length (AL), corneal curvature (K1 and K2), central anterior chamber depth (CACD), slit-lamp examination, dilated-pupil fundus examination using three-mirror contact lens and OCTA (Optovue, Inc., Fremont, CA, USA). AL, K1, K2, and CACD were measured using IOLMaster (Carl Zeiss Meditec, Inc., Dublin, CA, USA). The right eye of the individuals was designated for the studies, while the left eye was chosen only if the right eye satisfied any of the exclusion criteria. The inclusion criteria included an age between 18 and 40 years and a logMAR BCVA of the included eye of not more than 0. The exclusion criteria were as follows: (1) intraocular pressure greater than 21 mm Hg; (2) dioptric media opacity caused by corneal diseases, cataracts, and others which may affect refraction or imaging; (3) previous and existing intraocular diseases such as all kinds of retinal diseases (myopia-related and non-myopic-related retinal diseases), glaucoma, optic neuropathy, and uveitis; (4) pathologic myopia (such as diffuse atrophy, patchy atrophy, lacquer cracks, choroidal neovascularization, and etc.); (5) previous refractive and ocular surgeries or use of corneal contact lenses in the last 3 months; and (6) serious systemic diseases. The included eyes were divided into three groups according to the spherical equivalent (SE) and AL: low myopia (LM) (≤ −3.00 D ≤ SE ≤ −0.50 D), moderate myopia (MM) (−6.00 D ≤ SE < −3.00 D), and HM (≤ −9.00 D ≤ SE < −6.00 D or AL > 26 mm).

**OCT and OCTA Images**

OCT and OCTA images were acquired with pupils dilated using a commercial OCTA device and the AngioVue software 2.0. OCTA can capture images with a speed of 70,000 A-scans/second and a wavelength of 840 nm. The split-spectrum amplitude-decorrelation angiography algorithm was adopted to analyze the scans. Macular images (6 mm × 6 mm) and peripapillary images (4.5 × 4.5 mm) were captured simultaneously in the same individual. A senior ophthalmologist checked all the images' scan quality and segmentations. OCT and OCTA images with a scan quality less than 8 were excluded, and images with incorrect automatic segmentations were corrected. Afterward, the densities and thicknesses of the macular and peripapillary zones, including the foveal avascular zone (FAZ) area, superficial vascular plexus (SVP) density, deep vascular plexus (DVP) density, ganglion cell complex (GCC) thickness, full retinal thickness, radial peripapillary capillary plexus (RPCP) density, and retinal nerve fiber layer (RNFL) thickness, were automatically exported. Detailed OCT and OCTA measurements are presented in Figure 1.

**Statistical Analysis**

The commercial statistical software SPSS 24.0 (SPSS Inc. Chicago, IL, USA) was employed to perform statistical analyses. One-way ANOVA was performed to analyze the normally distributed numerical variables among the LM, MM, and HM groups, and Bonferroni’s post hoc analysis was employed to assess the significant differences between each pair of groups. The Kruskal-Wallis test was applied to analyze the nonnormally distributed numerical variables, and the χ2 test was performed to analyze the categorical variables. A value of p < 0.05 was defined as statistically significant. Correlations between major OCT/OCTA variables (FAZ area, SVP and DVP density, GCC, and full retinal thickness in the foveal, parafoveal, and perifoveal areas) and SE/AL were determined using Pearson correlation tests. Scatterplots were then generated using GraphPad Prism software 7.0 (GraphPad Software, San Diego, CA, USA). Afterward, major OCT/OCTA variables with sta-
Statistical significance were shown and included in a stepwise multiple linear regression analysis with adjustment for sex and age because sex and age were reported to be confounding factors for OCTA analyses in previous studies [15, 16].

Results

Patient Characteristics

In this study, 143 eyes of 143 myopic subjects were reviewed initially and 20 eyes were excluded. Among these excluded eyes, 3 were suspected glaucoma, 2 were cataract, 1 was macular epiretinal membranes, 5 had a history of ocular diseases or ocular surgeries which may affect refraction or imaging, and 9 had an OCTA scan quality of less than 8. Finally, 123 eyes (25 LM, 58 MM, and 40 HM) of 123 myopic subjects were included. The HM group had significantly higher SE and longer AL than those of the LM and MM groups (all \( p < 0.001 \)). The MM group also had a significantly higher SE and longer AL than those of the LM group (\( p < 0.001 \)). In addition, significantly greater K2 (\( p = 0.041 \)) and CACD (\( p = 0.005 \)) were observed in the HM group than in the LM group. No significant

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**Fig. 1.** OCT and OCTA measurements. a Scanning laser ophthalmoscope image in the macular area. b Foveal avascular zone area: area surrounded by the inner yellow line. c Superficial vascular plexus density. d DVP density. e Ganglion cell complex thickness. f Full retinal thickness. c, d \( \times 66 \) mm OCTA image in the macular zone. e, f \( \times 66 \) mm OCT thickness map in the macular zone. g \( \times 66 \) mm OCT B-scan image in the macular zone. c, e Correspondent to the area between red and green lines in (g). d Correspondent to the area between green and blue lines in (g). f Correspondent to the area between red and black lines in (g). c–f Foveal area (ring diameter = 1 mm): area inside the inner ring, parafoveal area (ring diameter = 3 mm): area between the middle and inner rings, perifoveal area (ring diameter = 6 mm): area between the middle and outer rings; the rings were divided into four sectors, S: superior, I: inferior, T: temporal, N: nasal. h Scanning laser ophthalmoscope image in the peripapillary zone. i Radial peripapillary capillary plexus density of a 4.5 \( \times 4.5 \) mm OCTA image. j Retinal nerve fiber layer thickness in an optic nerve head (ONH) map. k OCT B-scan image in the peripapillary zone. i, j Correspondent to the area between red and green lines in (k); inside disc: area inside the inner ring, peripapillary: area between two rings. The rings were divided into eight sectors: NS: nasal superior, NI: nasal inferior, IN: inferior nasal, IT: inferior temporal, TI: temporal inferior, TS: temporal superior, ST: superior temporal, and SN: superior nasal.
### Table 1. Demographic and general ocular characteristics

|                   | LM    | MM    | HM    | LM versus MM, p value | MM versus HM, p value | LM versus HM, p value |
|-------------------|-------|-------|-------|-----------------------|-----------------------|-----------------------|
| Eye, n            | 25    | 58    | 40    | NA                    | NA                    | NA                    |
| Age, years        | 26.80±2.89 | 26.21±2.13 | 26.30±2.81 | 0.328 | 0.858 | 0.439 |
| Sex (male/female) | 5:20  | 14:44 | 11:29 | χ² = 0.473, p = 0.789 |                       |                       |
| logMAR BCVA       | 1.19±0.04 | 1.17±0.08 | 1.15±0.12 | 0.201 | 0.463 | 0.074 |
| SE, D             | −1.99±0.62 | −4.70±0.84 | −7.45±0.93 | <0.001* | <0.001* | <0.001* |
| AL, mm            | 24.51±0.85 | 25.37±1.50 | 26.41±1.44 | <0.001* | <0.001* | <0.001* |
| K1, D             | 42.89±1.20 | 42.90±1.50 | 43.06±1.44 | 0.993 | 0.574 | 0.644 |
| K2, D             | 43.54±1.23 | 44.10±1.65 | 44.34±1.44 | 0.124 | 0.447 | 0.041* |
| CACD, mm          | 3.59±0.28 | 3.67±0.22 | 3.77±0.25 | 0.151 | 0.064 | 0.005* |

LM, low myopia; MM, moderate myopia; HM, high myopia; NA, not available; BCVA, best-corrected visual acuity; SE, spherical equivalent; D, dioptre; AL, axial length; K1, K2, corneal curvature; CACD, central anterior chamber depth. * p < 0.05.

### Table 2. Retinal vessel measurements in the macular zone

|                   | LM    | MM    | HM    | LM versus MM, p value | MM versus HM, p value | LM versus HM, p value |
|-------------------|-------|-------|-------|-----------------------|-----------------------|-----------------------|
| FAZ area, mm²     | 0.31±0.08 | 0.30±0.10 | 0.26±0.073 | 0.424 | **0.032*** | **0.014*** |
| SVP density, %    |       |       |       |                       |                       |                       |
| Whole image       | 50.21±2.86 | 48.72±3.73 | 48.15±3.58 | 0.081 | 0.430 | **0.023*** |
| Foveal            | 18.89±6.25 | 18.42±6.12 | 19.66±4.87 | 0.735 | 0.301 | 0.603 |
| Parafoveal        | 52.45±3.69 | 50.66±5.00 | 50.18±4.81 | 0.115 | 0.625 | 0.061 |
| Temporal          | 52.11±3.75 | 50.70±5.33 | 50.80±5.22 | 0.242 | 0.923 | 0.307 |
| Superior          | 52.73±4.49 | 51.88±5.74 | 51.45±4.88 | 0.499 | 0.690 | 0.339 |
| Nasal             | 50.89±3.66 | 49.96±5.45 | 49.57±5.09 | 0.439 | 0.709 | 0.303 |
| Inferior          | 52.00±5.03 | 50.32±5.10 | 50.37±5.20 | 0.175 | 0.961 | 0.215 |
| Perifoveal        | 50.58±3.23 | 49.47±3.66 | 49.06±3.50 | 0.191 | 0.569 | 0.092 |
| Temporal          | 45.67±3.70 | 43.56±4.46 | 43.29±4.69 | **0.048*** | 0.767 | **0.036*** |
| Superior          | 51.04±3.93 | 50.29±4.24 | 50.23±4.36 | 0.460 | 0.949 | 0.455 |
| Nasal             | 55.20±3.20 | 54.11±3.97 | 53.95±3.15 | 0.206 | 0.830 | 0.173 |
| Inferior          | 49.82±3.46 | 49.48±3.67 | 48.79±3.50 | 0.682 | 0.355 | 0.257 |
| DVP density, %    |       |       |       |                       |                       |                       |
| Whole image       | 49.35±5.24 | 47.88±5.94 | 45.75±4.65 | 0.256 | 0.059 | **0.010*** |
| Foveal            | 36.19±6.70 | 36.04±7.64 | 38.19±5.79 | 0.930 | 0.134 | 0.258 |
| Parafoveal        | 56.46±3.02 | 54.62±4.11 | 52.77±4.15 | 0.053 | **0.024*** | <0.001* |
| Temporal          | 58.43±2.57 | 56.38±3.88 | 55.86±3.45 | **0.016*** | 0.471 | **0.005*** |
| Superior          | 56.38±3.25 | 54.02±4.70 | 51.87±4.91 | 0.032* | **0.023*** | <0.001* |
| Nasal             | 57.30±3.23 | 55.62±3.78 | 54.55±3.28 | **0.048*** | 0.144 | **0.003*** |
| Inferior          | 54.94±3.60 | 53.11±5.68 | 49.56±6.24 | 0.169 | **0.002*** | <0.001* |
| Perifoveal        | 51.48±3.33 | 48.67±6.16 | 45.70±5.52 | **0.040*** | **0.012*** | **0.001*** |
| Temporal          | 54.25±3.38 | 50.27±6.13 | 48.28±5.46 | **0.003*** | 0.080 | <0.001* |
| Superior          | 53.34±4.34 | 50.13±6.52 | 46.87±6.66 | **0.033*** | **0.012*** | **0.001*** |
| Nasal             | 49.79±5.72 | 48.62±6.69 | 45.42±5.83 | 0.435 | **0.014*** | 0.007* |
| Inferior          | 48.39±5.68 | 45.71±7.53 | 42.29±5.61 | 0.092 | **0.013*** | <0.001* |

LM, low myopia; MM, moderate myopia; HM, high myopia; FAZ, foveal avascular zone; SVP, superficial vascular plexus; DVP, deep vascular plexus. * p < 0.05.
differences among the three groups were found in age, sex, logMAR BCVA, or K1. Details are presented in Table 1.

**OCTA Findings**

Compared to the LM or MM group, a significantly reduced FAZ area was noticed in the HM group (p < 0.05). In most sectors of the parafoveal and perifoveal areas, the HM group had a significantly lower DVP density and full retinal thickness than the LM and MM groups (all p < 0.05). Moreover, in some sectors of the parafoveal and perifoveal areas, a lower DVP density was also found in the MM group than in the LM group (all p < 0.05). However, significant differences were observed among the three groups in only one or several sectors with regard to SVP density, GCC thickness, and RNFL thickness, while no significant difference was noted among the three groups in any sector for RPCP density. Details are shown in Tables 2–4.

In Pearson correlation tests between major OCT/OCTA variables and SE, FAZ area (r = 0.246, p = 0.006), parafoveal DVP density (r = 0.288, p = 0.001), perifoveal DVP density (r = 0.314, p < 0.001), parafoveal full retinal thickness (r = 0.296, p = 0.001), and perifoveal full retinal thickness (r = 0.388, p < 0.001) were positively associated with SE, which was consistent with the results of Tables 2–4. Scatterplots showing the relationship between major OCT/OCTA variables and SE are shown in Figure 2.

Thereafter, the FAZ area, parafoveal DVP density, perifoveal DVP density, parafoveal full retinal thickness, and perifoveal full retinal thickness were included in a step-wise multiple linear regression analysis adjusted for sex and age. Perifoveal DVP density (β = 0.242, p = 0.005) and perifoveal full retinal thickness (β = 0.336, p < 0.001) were finally included and were positively associated with SE in this regression model.

In Pearson correlation tests between major OCT/OCTA variables and AL, FAZ area (r = −0.213, p = 0.019),

| Table 3. Retinal thickness measurements in the macular zone |
|------------------|------------------|------------------|------------------|
|                  | LM               | MM               | HM               |
| Whole image      | 102.25±7.33      | 102.42±5.61      | 99.70±5.81       |
| Foveal           | 51.26±7.29       | 52.34±6.23       | 53.44±6.34       |
| Parafoveal       | 109.06±6.81      | 109.46±6.47      | 108.17±5.02      |
| Temporal         | 100.59±6.73      | 101.38±6.11      | 99.89±5.01       |
| Superior         | 112.23±7.02      | 112.89±6.42      | 111.98±5.35      |
| Nasal            | 110.63±6.71      | 110.54±7.45      | 110.08±5.57      |
| Inferior         | 112.88±7.50      | 113.12±6.90      | 110.83±5.23      |
| Perifoveal       | 102.12±8.10      | 102.18±5.81      | 98.92±6.67       |
| Temporal         | 85.35±5.61       | 85.82±4.74       | 81.09±5.40       |
| Superior         | 101.66±8.39      | 101.89±5.95      | 97.74±6.82       |
| Nasal            | 120.43±10.77     | 120.84±8.12      | 119.18±8.56      |
| Inferior         | 101.20±9.43      | 100.41±7.44      | 97.82±8.95       |

|                  | LM               | MM               | HM               |
| Whole image      | 293.76±12.39     | 290.36±10.03     | 282.06±11.70     |
| Foveal           | 241.77±17.42     | 243.89±17.21     | 242.98±14.39     |
| Parafoveal       | 323.87±12.07     | 320.28±11.29     | 314.75±11.95     |
| Temporal         | 312.80±12.56     | 310.02±10.91     | 305.18±11.56     |
| Superior         | 328.51±12.61     | 325.16±11.30     | 319.87±12.26     |
| Nasal            | 329.70±12.12     | 325.26±12.61     | 320.47±13.37     |
| Inferior         | 324.58±12.44     | 320.80±12.29     | 313.54±11.92     |
| Perifoveal       | 286.74±13.97     | 283.17±10.34     | 273.77±12.59     |
| Temporal         | 270.40±10.66     | 266.56±9.25      | 256.63±13.12     |
| Superior         | 291.18±12.44     | 287.77±11.36     | 276.70±14.23     |
| Nasal            | 306.24±27.81     | 305.22±13.69     | 297.52±16.13     |
| Inferior         | 279.29±13.43     | 273.41±11.09     | 264.44±12.13     |

|                  | LM versus MM, p value | MM versus HM, p value | LM versus HM, p value |
| Whole image      | 0.032*               | 0.102               |
| Foveal           | 0.476                | 0.256               |
| Parafoveal       | 0.307                | 0.568               |
| Temporal         | 0.225                | 0.644               |
| Superior         | 0.475                | 0.874               |
| Nasal            | 0.740                | 0.749               |
| Inferior         | 0.092                | 0.221               |
| Perifoveal       | 0.018*               | 0.060               |
| Temporal         | <0.001*              | 0.002*              |
| Superior         | 0.004*               | 0.025*              |
| Nasal            | 0.366                | 0.581               |
| Inferior         | 0.136                | 0.116               |

LM, low myopia; MM, moderate myopia; HM, high myopia; GCC, ganglion cell complex. * p < 0.05.
parafoveal DVP density ($r = -0.257, p = 0.004$), perifoveal DVP density ($r = -0.228, p = 0.012$), parafoveal full retinal thickness ($r = -0.212, p = 0.019$), perifoveal full retinal thickness ($r = -0.455, p < 0.001$), and perifoveal GCC retinal thickness ($r = -0.186, p = 0.041$) were negatively associated with SE, which was also consistent with the results of Tables 2–4. Scatterplots showing the relationship between major OCT/OCTA variables and AL are shown in Figure 3. Thereafter, these OCT/OCTA variables were included in a stepwise multiple linear regression analysis adjusted for sex and age. Perifoveal DVP density ($\beta = -0.173, p = 0.020$) and perifoveal full retinal thickness ($\beta = -0.749, p < 0.001$) were finally included and were negatively associated with AL in this regression model.

In Figure 4, the HM group had more obvious and diffuse microvascular alterations (dark blue area in A2, B2, and C2) and thinner retinal thickness (A3, B3, and C3) than those of the MM and LM groups. Moreover, 2 eyes with dome-shaped macula (DSM) were observed in the HM group, while no DSM was noticed in other groups.

**Discussion**

In our study, the microvascular densities of different sectors and rings in the macular area were significantly decreased in HM eyes compared to MM or LM eyes. We speculate that vascular endothelial growth factor (VEGF) may contribute to reduced microvascular densities because some researchers [17, 18] found that VEGF negatively correlated with AL. It is possible that degeneration of retinal vascular endothelial cells and retinal pigment epithelial cells caused by retinal thinning during the progression of myopia may result in reduced VEGF production and microvascular densities. Nevertheless, reduced microvascular density mainly existed in the DVP, while it was not obvious in the SVP. Similarly, Cheng et al. [14] study also revealed that the DVP density was most related to retinal capillary loss in myopia. The underlying mechanism may contribute to the structure and role of the DVP. The SVP is a capillary network directly connected to retinal vessels, but the DVP is not directly connected to retinal vessels and is composed of separated lobular capillaries [19]. Therefore, the DVP may have compara-

**Table 4. Retinal vessel and thickness measurements in the peripapillary zone**

|          | LM            | MM            | HM            | LM versus MM, p value | MM versus HM, p value | LM versus HM, p value |
|----------|---------------|---------------|---------------|-----------------------|-----------------------|-----------------------|
| RPCP density, % |               |               |               |                       |                       |                       |
| Whole image | 50.29±2.10    | 49.95±2.08    | 49.29±2.83    | 0.550                 | 0.172                 | 0.097                 |
| Inside disc | 55.80±4.15    | 56.87±3.50    | 57.39±4.02    | 0.244                 | 0.513                 | 0.105                 |
| Peripapillary | 51.20±3.59    | 51.48±2.70    | 50.59±3.39    | 0.718                 | 0.177                 | 0.446                 |
| Nasal superior | 46.60±6.15    | 46.14±5.43    | 45.91±5.93    | 0.739                 | 0.846                 | 0.638                 |
| Nasal inferior | 45.38±5.76    | 45.36±5.46    | 44.86±6.76    | 0.988                 | 0.694                 | 0.738                 |
| Inferior nasal | 48.00±4.77    | 48.57±4.92    | 47.89±4.76    | 0.627                 | 0.501                 | 0.930                 |
| Inferior temporal | 57.50±4.06    | 56.37±3.67    | 56.01±3.59    | 0.210                 | 0.644                 | 0.121                 |
| Temporal inferior | 53.17±3.07    | 53.80±4.64    | 53.33±5.44    | 0.572                 | 0.628                 | 0.889                 |
| Temporal superior | 57.95±2.97    | 57.44±3.39    | 57.27±3.38    | 0.522                 | 0.804                 | 0.422                 |
| Superior temporal | 50.92±7.36    | 53.41±3.60    | 49.97±6.43    | 0.063                 | 0.003                 | 0.504                 |
| Superior nasal | 47.90±7.73    | 49.70±4.30    | 48.09±6.80    | 0.213                 | 0.199                 | 0.902                 |

| Peripapillary RNFL thickness, μm | Whole peripapillary | Nasal superior | Nasal inferior | Inferior nasal | Inferior temporal | Temporal inferior | Temporal superior | Superior temporal | Superior nasal |
|---------------------------------|---------------------|----------------|----------------|----------------|------------------|------------------|------------------|------------------|--------------|
| Whole peripapillary             | 122.89±12.00        | 114.80±26.60   | 98.07±23.41    | 140.71±19.86   | 168.88±21.13    | 78.65±11.54     | 93.33±10.29     | 158.50±16.48   | 135.48±21.51 |
| Nasal superior                   | 124.43±19.27        | 112.22±40.52   | 96.17±30.91    | 136.80±32.94   | 167.74±20.12    | 84.69±12.94     | 100.21±17.99    | 159.75±22.11   | 136.93±32.26 |
| Nasal inferior                   | 116.52±14.70        | 98.92±35.03    | 86.29±33.89    | 122.80±30.43   | 158.67±26.44    | 87.18±17.87     | 101.80±22.89    | 146.71±23.14   | 123.54±25.05 |
| Inferior nasal                   | 0.699               | 0.768          | 0.796          | 0.587          | 0.833            | 0.085           | 0.126           | 0.808           | 0.830        |
| Inferior temporal                | 0.024               | 0.081          | 0.124          | 0.025*         | 0.054            | 0.407           | 0.067           | 0.004*          | 0.024*       |
| Temporal inferior                | 0.135               | 0.090          | 0.135          | 0.020*         | 0.078            | 0.023*          | 0.077           | 0.034*          | 0.100        |
| Temporal superior                | 0.020*              | 0.023*         | 0.079          | 0.020*         | 0.023*           | 0.020*          | 0.077           | 0.034*          | 0.100        |
| Superior temporal                | 0.004*              | 0.034*         | 0.023*         | 0.004*         | 0.004*           | 0.023*          | 0.077           | 0.034*          | 0.100        |
| Superior nasal                   | 0.100               | 0.090          | 0.077          | 0.100          | 0.100            | 0.100           | 0.100           | 0.100          | 0.100        |

LM, low myopia; MM, moderate myopia; HM, high myopia; RPCP, radial peripapillary capillary plexus; RNFL, retinal nerve fiber layer. * p < 0.05.
Fig. 2. Scatterplots showing the relationship between the SE and OCT/OCTA variables. a FAZ area. b Parafoveal DVP density. c Perifoveal DVP density. d Parafoveal full retinal thickness. e Perifoveal full retinal thickness. SE, spherical equivalent; FAZ, foveal avascular zone area; DVP, deep vascular plexus; r, Pearson correlation coefficient.

Fig. 3. Scatterplots showing the relationship between the AL and OCT/OCTA variables. a FAZ area. b Parafoveal DVP density. c Perifoveal DVP density. d Parafoveal full retinal thickness. e Perifoveal full retinal thickness. f Perifoveal GCC thickness. SE, spherical equivalent; FAZ, foveal avascular zone area; DVP, deep vascular plexus; GCC, ganglion cell complex; r, Pearson correlation coefficient.
tively weaker regulatory capacity and may be more vulnerable during the progression of myopia. Moreover, the DVP partly contributes to the oxygen and metabolic consumption of the outer retina [20]. Some researchers [21, 22] suggested that, as disruption of the choroidal and outer retinal layers develops during the progression of myopia, the outer retinal layer may become thinner and have reduced oxygen and metabolic consumption. Thus, DVP density may be further decreased. Conversely, we speculate that the microvascular changes may precede the thickness changes. This is because in our study, the DVP density was significantly reduced in MM eyes compared to LM eyes, while the retinal thickness was not significantly different between LM and MM eyes. In addition, the full retinal thickness of most sectors in the macular area was significantly decreased in HM eyes compared to

Fig. 4. Retinal vessel densities and thickness differences in the three myopia groups. **a** Low myopia. **b** MM. **c** High myopia. (1) Scanning laser ophthalmoscope image in the macular area; (2) deep vascular plexus density; (3) full retinal thickness.
MM or LM eyes. However, the outer retinal thickness seemed to be affected more than the inner retinal thickness (GCC thickness). This may be due to outer retinal dysfunction secondary to choroidal disruption, as these two layers are close in proximity, and their relationship may be interlinked [23]. Correspondingly, along with the reduction in DVP density, decreased oxygen and metabolic consumption may accelerate outer retinal shrinkage [21].

In contrast to our results, Al-Sheikh et al. [21] found that both the SVP and DVP density decreased in myopic individuals. The difference between Al-Sheikh et al. [21] and our study may be due to the control group selection. Individuals without myopia were not included in our study, whereas these individuals were included in Al-Sheikh et al. [21] study. In addition, the mean SE in Al-Sheikh et al. [21] study was −8.29 ± 2.94 D, and the mean SE of HM eyes in our study was −7.45 ± 0.93 D, which suggested that the overall SE was higher in Sheikh’s study than in our study. Therefore, the reduction in microvascular density may start from the DVP and develop in both the SVP and DVP. With regard to the reason for reduced microvascular density, some [11] attributed it to microvascular loss, and others attributed it to narrowing and stretching of the retinal vessel caused by axial elongation of the eyeball [21, 24]. Conversely, Zhu et al. [11] study revealed that DVP densities in the high and superhigh myopia groups were significantly higher than those in the MM group and controls. This might be associated with a compensatory response. Dilated DVPs in dark adaptation help to maximize oxygen delivery to dark-adapted photoreceptors [25]. Nevertheless, clear mechanisms await validation through further research.

A reduced FAZ area was noticed in HM individuals compared to non-HM individuals, which was an interesting finding. Li et al. [26] and Milani et al. [27] observed no significant difference between the HM and non-HM groups with regard to the FAZ area. Ocular magnification was corrected using Bennett’s formula in Li et al. [26] study. Since AL may to some degree affect ocular magnification, AL can cause some errors during laser ophthalmoscopy measurements [28]. However, correction was not done in Milani et al. [27] and our study. Therefore, in addition to AL, some other confounding factors, such as blood flow velocity, may also exert an influence on FAZ area and density assessments. According to Shimada et al. [24] report, retinal blood flow velocity decreased in HM. Since OCTA cannot distinguish if blood flow is too fast or too slow, the variation in velocity may also affect the FAZ area and density assessments.

Another interesting finding was that the parafoveal and perifoveal density/thickness reduction was more significant than the foveal density/thickness reduction. Moreover, in our regression analysis adjusted for sex and age, perifoveal density/thickness was significantly positively related to SE and was significantly negatively related to AL. These paralleled results jointly support our hypothesis that the DVP density may be closely related to myopic severity. Our results were quite consistent with Cheng et al. [14] study. The major difference between Cheng et al. [14] and our study is that Cheng only included HM individuals, while we included both MM and HM individuals. Therefore, we may slightly extend their conclusion: perifoveal DVP density may be an indicator of microvascular network loss in all myopia, not only in HM. To ensure the central retina’s nutrition and functions, a reduction in the vasculature and thickness may occur in the perifoveal region prior to the center [29]. Therefore, perifoveal density/thickness may be valuable in evaluating the retinal microvasculature of myopia.

With regard to the RPCP density and RNFL thickness, no significant difference was noticed in the density, while significant differences could only be noticed in the thickness in a few sectors. Although the microvasculature in myopic individuals has been discussed in many studies, there are only a limited number of studies providing evidence on the RPCP density. In He et al. [30] study, the classification was quite similar to our study. No significant difference was noticed among the different groups in RNFL thickness, while the RPCP density of MM and HM eyes was significantly reduced compared to that of LM eyes. MM, HM, and control eyes were compared in Qu et al. [31] research, and significantly reduced RNFL thickness was noticed only in HM eyes compared to control eyes. Whether pathological myopia was included was not illustrated in He et al. [30] or Qu et al. [31] study. Yaprak and Yaprak [13] compared HM and control eyes, and both the RPCP density and RNFL thickness were significantly reduced in the HM group. The HM subjects in Yaprak’s study were all non-pathological. The classification of myopia severity and whether pathological myopia is included may cause variations in the results. However, the influence of pathological myopia on OCTA variables also depends on the location and layer of the lesions.

In our study, 2 eyes with DSM were observed in the HM group, while no DSM was noticed in other groups. DSM is reported to be correlated with HM with posterior staphyloma in some studies, but its pathogenesis remains controversial [32, 33]. However, quantitative OCTA studies on DSM were relatively lacking and the number...
Some limitations existed in our study. First, similar to some other studies [13, 34, 35], magnification effects have not been corrected in our study and the actual values may be affected. According to the Littman and the modified Bennett formulae which has been adopted frequently to correct magnification effects in myopia-related studies, the actual area in vessel density measurement seemed to be smaller and closer to the fovea and the FAZ area seemed to be larger when they were compared to the original data, especially in moderate and HM [14, 36]. The correction may in some degrees lower the vessel densities and increase the FAZ area in patients with longer AL, which may further contribute significance to the difference between HM and non-HM groups. Another concern on correction of magnification effect was the clinical application. As AL cannot be automatically corrected by the present OCTA machines, and a series of complicated transformation have to be adopted to obtain the actual outcome. Our study established two models with regard to SE and AL using uncorrected data, respectively. In fact, his may provide evidence on microvasculature of myopic eyes from the perspective of clinical practice. It may be a clinically fitting way to some extent because we do not have to adopt complicated transformation when we assess OCTA data of myopic eyes in daily clinical application. Besides, the sample size was relatively small. Large-scale well-designed studies are awaiting to be performed. Moreover, imaging techniques may affect the detection of the flow rate. In addition to artefacts, directional changes in Henle fiber reflectivity might also affect imaging, especially in elongated eyes where the retina is tilted or even nonperpendicular to the OCT or OCTA scan in some positions [37]. However, imaging techniques are developing, and future improvements should be forthcoming.

**Conclusions**

The DVP density was closely related to the severity of myopia. Reduced perifoveal DVP density may be an indicator of microvascular network loss in myopia. OCTA may provide useful and crucial information for monitoring the progression of myopia.

**Statement of Ethics**

This study was approved by the Ethics Committee of Ningbo Eye Hospital (approval number: 2019-QTKY-21). As this was a retrospective study, the study has been granted an exemption from requiring written informed consent from the above ethics committees.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Hongyan Yao: data collection, image editing, and manuscript drafting; Danli Xin: data analysis; Zijing Li: data analysis, image editing, and manuscript drafting.

**Data Availability Statement**

Data will be provided at the request of readers.

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