· Original article ·

The distribution characteristics of retinal nerve fiber layer thickness in macular area and its relationship with vessel density in highly myopic eyes

Huan Chen[1,2]*，Chen Chen[1,2]*，Qin Long[1,2]

[1]Department of Ophthalmology，Peking Union Medical College Hospital，Chinese Academy of Medical Sciences，Beijing 100073，China
[2]Key Laboratory of Ocular Fundus Diseases，Chinese Academy of Medical Sciences & Peking Union Medical College，Beijing 100073，China
Co-first authors：Huan Chen and Chen Chen
Correspondence to：Qin Long. Department of Ophthalmology，Peking Union Medical College Hospital，Chinese Academy of Medical Sciences，Beijing 100073，China；Key Laboratory of Ocular Fundus Diseases，Chinese Academy of Medical Sciences & Peking Union Medical College，Beijing 100073，China. longqinbj@ hotmail.com

高度近视眼黄斑区神经纤维层厚度分布特点及其与血流密度的关系

陈　欢[1,2]*，陈　晨[1,2]*，龙　琴[1,2]

摘要

目的：研究高度近视眼黄斑区神经纤维层厚度和血流密度的分布特点并分析其相关因素。

方法：收集高度近视患者 20 例 40 眼,年龄为 29.90±7.92 岁,等效球镜屈光度为 -8.95±2.01 D。采用光学相干断层扫描血管成像技术（OCTA）测量黄斑区神经纤维层厚度,获取视网膜浅层毛细血管层、视网膜深层毛细血管层及脉络膜毛细血管层的血流分布图像并计算各层血流密度。直径 6 mm 的黄斑区分为 9 个亚区域：黄斑中心凹区,旁中心凹区和中心凹外区各自分为上方、下方、鼻侧和颞侧 4 个象限。比较黄斑不同亚区域的神经纤维层厚度的差别,分析其与屈光度、眼轴、各层血流密度的关系。

结果：旁中心凹区的 4 个象限中,上方神经纤维厚度最低,下方神经纤维厚度最高（均 $P<0.05$）。中心凹外区 4 个象限中颞侧神经纤维厚度最低（均 $P<0.05$）。中心凹外区上方神经纤维层厚度与屈光度存在负相关（$r= -0.356，P= 0.024$）。视网膜浅层毛细血管层的血流密度与旁中心凹区鼻侧和下方象限,以及中心凹外区上方、鼻侧和下方象限的神经纤维层厚度呈正相关（$r=0.314、0.408、0.467、0.655、0.737$,均 $P<0.05$）；脉络膜毛细血管层血流密度与中心凹外区的上方象限呈负相关（$r=-0.356，P=0.024$）。

结论：高度近视眼黄斑区神经纤维层具有各象限不均匀分布特点。随着屈光度的增加,局部神经纤维层变薄,并且存在区域特异性,部分区域神经纤维层厚度的变化与视网膜浅层毛细血管丛及脉络膜毛细血管层的血流密度相关。

关键词：视网膜；高度近视；光学相干断层扫描血管成像技术；视网膜神经纤维层；黄斑血流密度

Abstract

• AIM：To investigate the distribution characteristics of retinal nerve fiber layer（RNFL）thickness and vessel density（VD）in macular area of eyes with high myopia（HM），using optical coherence tomography angiography（OCTA）.

• METHODS：Forty eyes in 20 patients diagnosed with HM，age 29.90±7.92 years old，with a spherical equivalent（SE）of -8.95±2.01 D，were recruited. The RNFL thickness and the VD of the superficial retinal capillary plexus（SCP），deep retinal capillary plexus，and choroidal capillary（CC）were measured by OCTA. Macular regions within a 6 mm diameter circle were divided into 9 subfields：the central subfield，and the pericentral and peripheral regions of superior，inferior，nasal，and temporal quadrants. The RNFL thickness of different subfields were compared，and their relationships with SE，axial length，and VD were analyzed.

• RESULTS：In the pericentral region，the RNFL thickness of the superior quadrant was the lowest，whereas thickness was highest in the inferior quadrant（all $P<0.05$）. In the peripheral region，the RNFL thickness of the temporal quadrant was the lowest（all $P<0.05$）. A negative correlation was found between the RNFL

thickness and SE（$r=-0.356$, $P=0.024$）in the peripheral superior subfield. The VD of SCP was positively correlated with RNFL thickness in the nasal and inferior quadrants of the pericentral region and in the superior, nasal, and inferior quadrants of the peripheral region（$r=0.314$, 0.408, 0.467, 0.655, and 0.737 respectively; all $P<0.05$）, whereas the VD of CC was negatively correlated with RNFL thickness in the peripheral superior subfield（$r=-0.356$, $P=0.024$）.

• CONCLUSION：The RNFL of macular areas is not uniformly distributed in HM. As the SE increases, the RNFL thickness decreases in certain areas, which correlates with the VD of SCP and CC layers.

• KEYWORDS：retina; high myopia; optical coherence tomography angiography; retinal nerve fiber layer; macular vessel density

INTRODUCTION

High myopia（HM）refers to refractive errors greater than -6 diopter（D）with an axial length（AL）greater than 26 mm and is often associated with an increased risk of multiple ocular impairments, which may develop into irreversible vision loss, due to various pathologic changes in the choroid and retina, especially the macula area[1]. However, due to the uncertainty of the pathogenesis, the treatment for myopic maculopathy, particularly macular atrophy, remains a major challenge in HM eyes.

The retinal nerve fiber layer（RNFL）consists of ganglion cell axons and plays an important role in the maintenance of physiological function in the retina and choroid[2]. Previous studies have revealed that the peripapillary RNFL thickness decreases and is negatively correlated with the myopic degree in patients with HM[3-5]. However, the characteristics of macular RNFL in HM patients and its relationship with the myopic degree have been poorly studied. Additionally, evidence suggests that the pathogenesis of macular atrophy can be ascribed to choroidal and retinal microcirculation disorders in the posterior pole, accompanied by excessive eye elongation in the HM eye[6-7]. However, the specific mechanism remains to be clarified.

Optical coherence tomography angiography（OCTA）is an advanced, noninvasive imaging technique that is capable of measuring the retinal and choroidal vessel networks in different layers by detecting erythrocytes flowing in blood vessels over time. With OCTA, the RNFL thickness and vessel density（VD）of different layers in the macular area can be obtained, simultaneously. The purpose of our study was to investigate the distribution characteristics of RNFL thickness and VD in the macular area of HM eyes, using OCTA, which may help us to better understand the pathogenesis of macular atrophy due to HM.

SUBJECTS AND METHODS

Subjects This study was approved by the Institutional Review Board of Peking Union Medical College Hospital. The methods were performed in accordance with the tenets of the Declaration of Helsinki. Patients with HM were randomly recruited from the Ophthalmology Department of Peking Union Medical College Hospital（Beijing, China）, from March 2019 to May 2019. A total of 40 eyes in 20 patients were included in this study. The inclusion criteria were as follows：1) spherical equivalent（SE）≤-6.00 D with AL≥26 mm; 2) clear optical media, with good fixation; 3) stable mental health, with the ability to understand the examination. The exclusion criteria were as follows：1) any type of ocular disorder in either eye, other than HM; 2) a history of intraocular surgery or ocular trauma; 3) a history of hypertension, diabetes mellitus, or other systemic diseases that may affect vessel diameter; 4) mental illness.

Patients underwent a detailed ophthalmic examination, including best-corrected visual acuity（BCVA）, intraocular pressure（IOP）measurement, a slit-lamp examination, and dilated fundus examination, by indirect ophthalmoscope. The refractive error value was represented by the spherical equivalent（SE）. The AL was measured with a coherence interferometry biometric measurement device（IOL Master; CarlZeiss Meditec, Oberkochen, Germany）.

OCTA Measurements and Data Analysis Spectralis OCTA（Version SP 6.9a; Spectralis Heidelberg Engineering, Heidelberg, Germany）was used in this study by the same investigator in every case to eliminate the possible interobserver variability. OCTA images were obtained, following pupil dilation, using a 6 mm×6 mm volume scan pattern centered on the fovea. The automated real-time mode was set to 35（frames averaged per B-scan）, and the scan was repeated twice to acquire the best images. A 6 mm×6 mm volume OCTA scan can provide a macular RNFL thickness map and automatically draw three concentric circles, with radii of 1.0 mm, 3.0 mm, and 6.0 mm relative to the fovea center, and nine subfields were defined using the Early Treatment Diabetic Retinopathy Study（ETDRS）grid：the central region（within the inner circle）; the pericentral superior, pericentral nasal, pericentral inferior, and pericentral temporal subfields（between the inner and middle circles）; and the peripheral superior, peripheral nasal, peripheral inferior, and peripheral temporal subfields（between the middle and outer circle）. The built-in software automatically calculated and generated an average RNFL thickness for each region.

En face images of the superficial retinal capillary plexus（SCP）, deep retinal capillary plexuses（DCP）, and choroidal capillary（CC）were visualized automatically by segmenting two separate slabs, which were defined by arbitrary segmentation lines created by the device software.
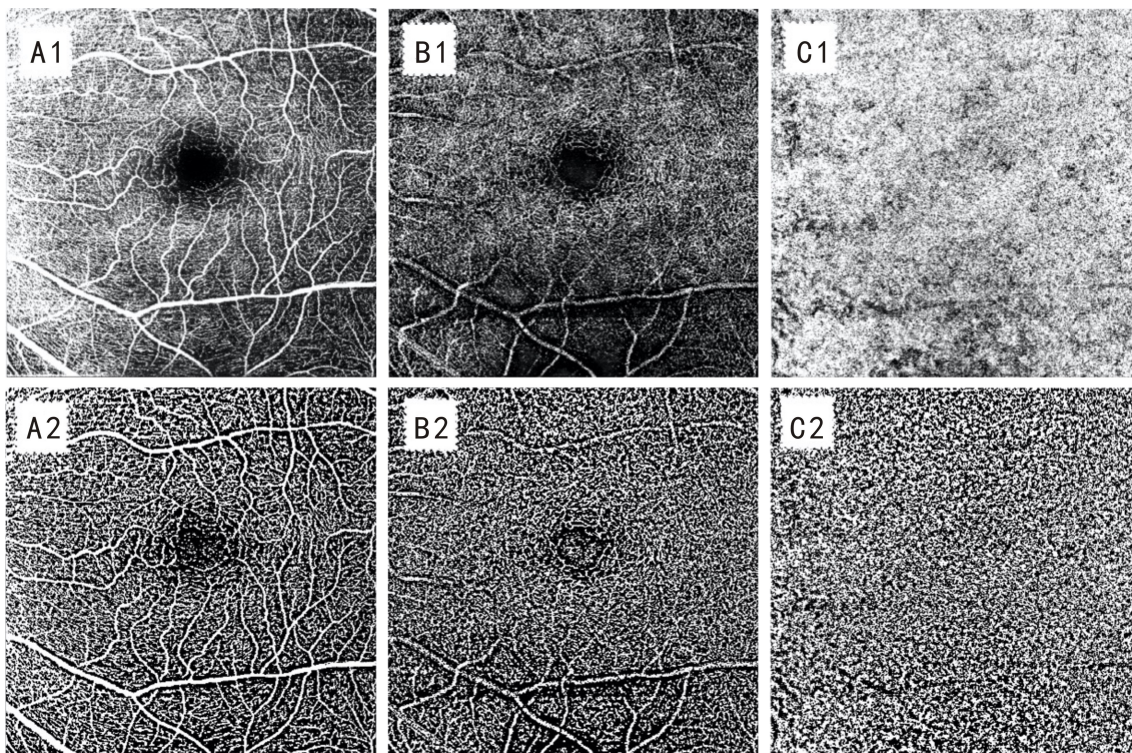
Figure 1 Example OCTA image and binarized images using Niblick's autolocal threshold technique in ImageJ software Figures A1, B1 and C1 are OCTA images of the SCP, DCP, and CC respectively; Figures A2, B2, and C2 are binarized images of SCP, DCP, and CC using local Niblack respectively.

VD was expressed as the proportion of the total measured area with a blood flow signal[7]. VDs of the macular SCP, DCP, and CC angiograms were measured by the same doctor, using a binarization technique in ImageJ software (version 1.49, National Institutes of Health, Bethesda, Maryland, USA). Niblick's autolocal threshold technique was adopted in our study, as previously described[8-9]. Figure 1 shows an example OCTA image and binarized images using Niblick's autolocal threshold technique in ImageJ software.

Statistical Analyses Data were analyzed using the statistical software IBM SPSS 19.0 for Windows (SPSS, Chicago, IL). The Shapiro–Wilk test was used to determine the normal distribution of the data. Numerical variables with normal distributions were presented as the mean±standard deviation (SD) and were compared using a one–way analysis of variance (ANOVA) and Tukey's post hoc tests. Numerical variables without normal distributions were presented as the median±quartile spacing, and a Kruskal–Wallis test was used for group comparisons. A Mann–Whitney U test was used to determine the differences among quadrants of the pericentral and peripheral regions. To evaluate the relationship between the RNFL thickness and macular VD profiles and between RNFL thickness and AL, Spearman's correlation analysis was used. A P-value of less than 0.05 was considered to be significant.

RESULTS

Demographic Overall, 20 subjects diagnosed with HM were recruited in this study, including 11 female and 9 male subjects, with a mean age of 29.90±7.92 (range: 21–41) years old, with a mean SE of −8.95±2.01 (range: −6.38

to −14.88) D, and a mean AL of 27.06±0.62 (range: 26.16−28.93) mm.

Macular RNFL Thickness Profiles The RNFL thicknesses in the central, pericentral, and peripheral regions were significantly different ($P < 0.001$). Pairwise comparisons showed that the RNFL thicknesses of the pericentral (89.50± 12.00) μm and peripheral (152.00±30.25) μm regions were thicker than that of the central region (14.00±4.75 μm) ($P< 0.001$) (Figure 2A). Further analysis of the quadrantal partitions showed that all quadrants in the pericentral regions had thinner RNFLs than the corresponding quadrants in the peripheral regions (all $P<0.05$; Table 1).

The RNFL thicknesses of the superior, inferior, nasal, and temporal quadrants of the pericentral region were significantly different (all $P<0.05$), and pairwise comparisons showed that the RNFL thickness of the superior quadrant was the lowest, whereas that in the inferior quadrant was the highest ($P < 0.05$) (Figure 2B). Similarly, significant differences were observed among the RNFL thicknesses of the four quadrants of the peripheral region ($P < 0.001$); pairwise comparisons revealed that the RNFL thickness of the temporal quadrant was the lowest, whereas the RNFL thickness of the nasal quadrant was significantly larger than those of the superior and temporal quadrants ($P < 0.05$) but was not significantly different compared with that of the inferior quadrant ($P = 0.603$) (Figure 2C).

Relationships Between Macular RNFL Thickness Profiles and SE or AL Spearman's correlation analysis showed that the RNFL thickness of the central region was not correlated with the SE or AL (all $P>0.05$). Similarly, in the pericentral
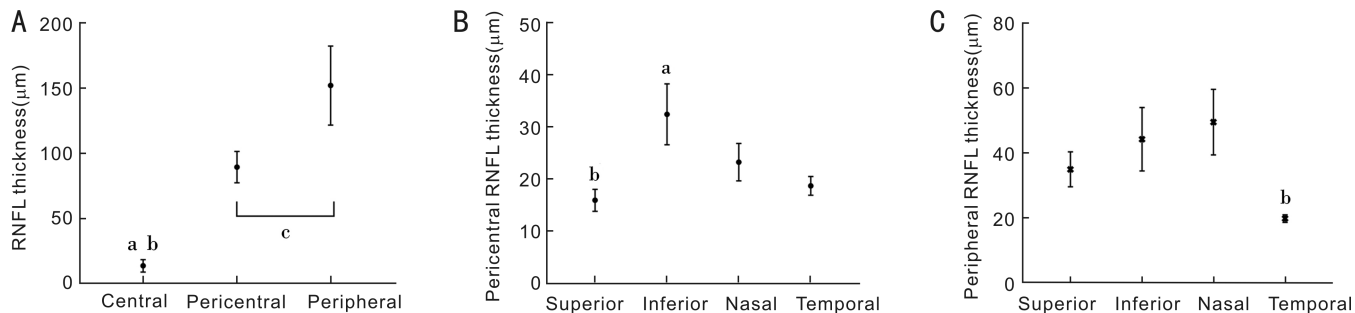
Figure 2　Comparisons of different regions of macular RNFL thickness A：RNFL thickness of the central, pericentral, and peripheral regions. [a]The comparison of total RNFL thickness between the central area and the pericentral area, $P<0.05$. [b]The comparison of total RNFL thickness between the central area and the peripheral areas, $P<0.05$. [c]The comparison of total RNFL thickness between the pericentral area and the peripheral area, $P<0.05$；B：The pericentral RNFL thickness in different quadrants. [a]Pairwise comparisons showed that the RNFL thickness of the inferior quadrant was the highest, $P<0.05$；[b]Pairwise comparisons showed that the RNFL thickness of the superior quadrant was the lowest, $P<0.05$；C：The peripheral RNFL thickness in different quadrants. [b]pairwise comparisons revealed that the RNFL thickness of the temporal quadrant was the lowest, $P<0.05$.

Table 1　Regional RNFL thickness in the pericentral and peripheral area　　　　　　　　　　　　　mean±SD

Parameters	RNFL thickness (μm)			
	Superior	Inferior	Nasal	Temporal
Pericentral	15.88±2.11	32.35±5.82[a]	23.18±3.57[a]	18.65±1.79
Peripheral	34.98±5.37[a]	44.23±9.73	49.50±10.07[a]	19.88±1.16
Z value	−7.673	−5.351	−7.267	−3.275
P value	<0.001	<0.001	<0.001	0.001

RNFL：Retinal nerve fiber layer；[a]For RNFL thickness without normal distributions, data were displaced as median±quartile spacing. Mann−Whitney U test was used to determine the differences among quadrants of the pericentral and peripheral regions；P-values less than 0.05 are considered significant and highlighted in bold.
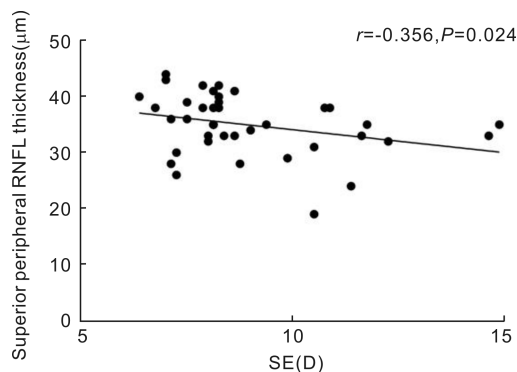
Figure 3　The RNFL thickness of the superior quadrant of the peripheral area was negatively correlated with the SE.

regions, no correlations were found between RNFL thickness in any quadrant and SE or AL (all $P>0.05$). In the peripheral region, the RNFL thickness of the superior quadrant was negatively correlated with SE ($r=-0.356$, $P=0.024$) (Figure 3), but RNFL thickness was not correlated with the SE or AL in any other quadrant (all $P>0.05$).

Relationships Between RNFL Thickness and VD in Different Layers In the central region, no correlations were found between RNFL thickness and the VD of the SCP, DCP, or CC (all $P>0.05$). In the pericentral region, the VD in the SCP was positively correlated with the RNFL thickness in the nasal and inferior quadrants ($r=0.314$ and 0.408, $P=0.048$ and 0.002, respectively). No correlations were found between RNFL thickness and the VD of the DCP in any quadrant. In

the peripheral region, correlations were found between the VD of the SCP and RNFL thickness in the superior, nasal, and inferior quadrants ($r=0.467$, 0.655, and 0.737; $P=0.002$, $P<0.001$, and $P<0.001$, respectively). However, no correlations were found between the RNFL thickness and the VDs for the DCP in any quadrant (all $P>0.05$) (Table 2). In contrast, a negative correlation was observed between the VD of the CC layer and RNFL thickness in the superior quadrant ($r=-0.356$, $P=0.024$).

DISCUSSION

In the present study, we found out that the RNFL thickness was unevenly distributed in the macular region of HM patients. As the SE increases, the RNFL thickness decreases in the peripheral superior subfield. The VD of SCP was positively correlated with RNFL in nasal and inferior quadrants of pericentral region and in the superior, nasal, and inferior quadrants of the peripheral region whereas the VD of CC was negatively correlated with RNFL thickness in the peripheral superior subfield.

Chorioretinal atrophy, especially in the macular region, is a primary manifestation of myopic maculopathy and is also a major cause of vision loss in HM eyes[10]. With the advantages of ultrahigh−resolution second−generation Spectralis OCTA, macular RNFL thicknesses in different regions and VDs in multiple layers were detected and analyzed in HM eyes to investigate the potential pathomechanisms underlying myopic maculopathy.

Table 2　Relationship between RNFL thickness and VD in the macular area

RNFL	SCP（VD）		DCP（VD）		CC（VD）	
	r	P	r	P	r	P
Central	0.027	0.866	0.015	0.927	0.163	0.315
Pericentral superior	−0.096	0.557	−0.216	0.180	−0.166	0.305
Pericentral nasal	0.314	0.048	−0.092	0.574	−0.104	0.523
Pericentral inferior	0.408	0.002	−0.098	0.549	−0.149	0.359
Pericentral temporal	0.104	0.525	0.042	0.799	0.071	0.661
Peripheral superior	0.467	0.002	−0.173	0.287	−0.356	0.024
Peripheral nasal	0.655	<0.001	−0.057	0.725	−0.209	0.195
Peripheral inferior	0.737	<0.001	−0.023	0.888	−0.143	0.378
Peripheral temporal	0.281	0.079	−0.141	0.384	−0.164	0.311

RNFL：Retinal nerve fiber layer；VD：Vessel density；SCP：Superficial retinal capillary plexus；DCP：Deep retinal capillary plexus；CC：Choroidal capillary；Spearman's correlation analysis was used to evaluate the relationship between the RNFL thickness and macular VD profiles in different regions；P-value less than 0.05 are considered significant and highlighted in bold.

Many studies have investigated structural changes in myopic eyes using OCTA, mainly the thinning of the peripapillary RNFL[11], and the impairment of the macular microvascular network[12], while found no correlation between peripapillary RNFL thickness and macular VD in HM eyes[13]. Only one literature addressed the difference of macular RNFL in the pericentral region in HM eyes compared to normal controls[14]. Till now, there is no report addressing the relationship between macular RNFL thickness and macular VD in HM eyes. Using Spectralis OCTA, we focused on macula, simultaneously observed the RNFL thickness profiles of different regions and the VD distribution of different layers, which can provide a more comprehensive picture of macular microstructure and help detecting the potential linkage underling macular neurotrophy and microvascular network in HM eyes. Our results indicated that different quadrants and subfields in macular region have different characteristics in term of RNFL thickness. Based on the subfield, macular RNFL thickness in eyes with HM gradually increased, from the central region to the pericentral and peripheral regions, which was accordant to the results of Liu et al[14], this distribution profile may result in the central region of macula more sensitive to myopic pathological injury, such as ischemia hypoxia induced by AL elongation in HM eyes. As to the quadrant, in the pericentral macula, the RNFL was found to be the thickest in the inferior and the thinnest in the superior quadrant, while in the pericentral macula, the RNFL thickness was the thickest in the nasal quadrant and the thinnest in the temporal quadrant. For the reasons causing the inhomogeneous RNFL thickness distribution, first, the RNFL anatomy may play an important role, in which the axons of retinal ganglion cells in the temporal macula pass through the superior and inferior maculopapular bundle and terminate at the optic disc, therefore, fewer retinal nerve fibers exist in the temporal quadrant than that of other quadrants in peripheral macular subfield as showed in our results. Second, in the HM eye, the unbalanced biomechanical stretching of the posterior sclera may further result in the observed heterogeneous profile of macular RNFL thickness across different quadrants and subfields[15-17]. Further analysis combining with other relative parameters, such as the regional eyeball expansion in HM eyes, are necessary to make more integrate explanation.

Correlation analysis showed that macular RNFL thickness in the superior peripheral region was negatively correlated with the myopic degree, which is in agreement with the results reported by previous studies[13-14]. Evidence has suggested that decreasing SE causes the chorioretinal to become hypoxic, which may cause the degeneration of retinal ganglion cell axons and, consequently, induce the thinning of the RNFL[18]. The thinning of the RNFL in the macula could further lead to myopic maculopathy, due to a lack of local neurotrophy.

In our study, a positive correlation was found between the VD of the SCP and the RNFL thickness in the nasal and inferior pericentral regions, as well as the superior, nasal, and inferior peripheral regions. Evidence showed that, in HM eyes, peripapillary RNFL dysfunction may cause a reduction in the oxygen supply and nutrient demand, resulting in further peripapillary VD loss[19], the macular VD in SCP was significantly lower in the HM eyes compared to normal controls[13,20], however, the relationship between macular RNFL and macular VD still need to be explored previous studies have demonstrated that HM might cause hypoxia and insufficient perfusion as the SE decreases and the AL increases[21], which may lead to the rupture of Bruch's membrane and changes in the retinal pigment epithelium （RPE）[22-23]. Hence, the elongation of the eye that occurs during HM leads to the thinning of the RNFL, due to the expansion of the posterior sclera, further stretching the capillaries in the macular area[24] and potentially damaging Bruch's membrane, which may further impair chorioretinal circulation in the posterior pole. A recent study demonstrated that the VD of the SCP and DCP were protective factors for diffused chorioretinal atrophy[25]. Therefore, excessive AL elongation, which mechanically stretches the retinal tissue, may result in decreased retinal thickness and the further degeneration of the retinal vascular endothelium and RPE; this process may also reduce the production of vascular endothelial growth factor （VEGF）, resulting in a relative decrease in VD, which may, consequently, induce the

progressive thinning of the chorioretinal thickness and macular atrophy in HM eyes.

As mentioned above, we found a positive correlation between macular RNFL thickness and the VD of the SCP, which is consistent with the histopathological changes observed during HM changes. Interestingly, our study showed a negative correlation between the VD of the CC and the RNFL thickness of the superior pericentral area, which may be related to the induction of secondary choroidal neovascularization (CNV) due to disruptions in microcirculation in HM eyes[23].

The primary limitations of our study are as follows:1) since the main purpose of our study was to investigate the comprehensive distribution characteristics of RNFL and its relationship with VD in macular area focusing on HM patients, thus, we didn't include normal control group in the current experimental design, further comparative studies involving healthy emmetropic subjects need to be conducted to improve and verify our research findings; 2) the sample size was relatively small; 3) although we found multiple characteristic profiles for macular RNFL, VD, and the relationship between these two factors in eyes with HM, implying a potential maculopathy mechanism that can be attributed to HM, the relationships between either RNFL or VD and concrete types of myopic maculopathy were not investigated in this study due to the small sample size.

In summary, the present study found that in eyes with HM, the RNFL is not equally distributed throughout the macular region. As the SE increases, the thickness of the RNFL decreases in the superior peripheral region, moreover, RNFL thickness was correlated to the macular VD of the SCP and CC layers. These characteristics of eyes with HM improve our understanding of the potential mechanisms that may be involved in the development of maculopathy due to HM, particularly macular atrophy. Further studies with larger sample sizes including emmetropic subjects are necessary before definite conclusions can be drawn.

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