Ocular and Hemodynamic Factors Contributing to the Central Visual Function in Glaucoma Patients With Myopia

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Purpose. The purpose of this study was to investigate the ocular and hemodynamic factors contributing to the central visual function in glaucoma patients with myopia.

Methods. This study was a prospective observational study, which included 236 eyes of 140 patients with normal-tension glaucoma (NTG), which includes 114 eyes with mild myopia (axial length ≥24 and <26 mm) and 122 eyes with moderate-to-severe myopia (axial length ≥26 mm). Ocular characteristics were axial length and posterior pole profiles, including peripapillary atrophy (PPA) to disc area ratio, disc tilt ratio, disc torsion, and disc-foveal angle. Hemodynamic factors included standard deviation of the mean of qualified normal-to-normal intervals (SDNN) of a heart rate variability (HRV) test and vessel density (VD) parameters from optical coherence tomography angiography (OCTA). The root mean square error was estimated as a measure of the VD fluctuation. Association between ocular characteristics and VD parameters of the OCTA with the central sensitivity of the 10-degree visual field or the presence of central scotoma were analyzed.

Results. Deep layer VD of the peripapillary and macular areas showed significant differences between mild and moderate-to-severe myopia ($P = 0.034$ and $P = 0.045$, respectively). Structural parameters, especially PPA to disc area ratio, had significant correlation with peripapillary VD parameters in myopic eyes. Lower SDNN value (ß = 0.924, $P = 0.011$), lower deep VD of the macular area (ß = 0.845, $P = 0.001$), and greater fluctuation of deep VD in the peripapillary area (ß = 1.517, $P = 0.005$) were associated with the presence of central scotoma in patients with glaucoma with myopia in multivariate logistic regression analysis.

Conclusions. The structural changes by myopia, especially in the peripapillary region, affected VD parameters in myopic eyes. Lower deep VD and greater VD fluctuation in the peripapillary region showed association with central scotoma in patients with glaucoma with myopia, suggesting both structural and vascular changes by myopia may be related to central visual function in glaucoma patients with myopia.

Keywords: open-angle glaucoma, optical coherence tomography angiography, visual field tests

Myopia is a well-known risk factor of glaucoma. Myopia is characterized by scleral changes due to an elongation of eyeball and this influences the structure of the optic nerve head (ONH).[1] These structural changes are thought to contribute to axonal damage that increases the risk of glaucoma in myopic eyes. The structural changes related to myopia have been evaluated by various methods and we previously measured the posterior scleral profiles, including optic disc tilt, torsion, disc-foveal angle, and peripapillary atrophy (PPA) to disc area ratio.[2,3] Among these structural factors, disc-foveal angle was one factor associated with central scotoma in patients with myopic glaucoma.[4] The PPA area that represents the stretching of the sclera temporal to the disc has also been related to central scotoma in patients with myopic glaucoma.[5–7] Additionally, stretching and elongation around the ONH and PPA by myopia may affect the blood flow within the ONH. Both systemic and ocular vascular dysregulation and perfusion have been considered as important factors in the progression of normal-tension glaucoma (NTG).[8–12] Decrease in blood flow and decrease vessel density (VD) using optic nerve optical tomography angiography (OCTA) has been reported in myopic eyes.[13–15] We have previously shown that decreased VD within the PPA region was related to glaucoma progression and the

presence of central scotoma in patients with myopic glaucoma. Therefore, both structural and vascular changes due to myopia could affect the retinal ganglion cells of the central visual field (VF) region. However, contributing risk factors to central visual function in myopic glaucoma has not been fully investigated.

Therefore, we purposed to evaluate the relationship between structural changes of the eyeball due to myopia and hemodynamic changes of the retinal layer to the presence of central scotoma in glaucomatous eyes with myopia to understand the pathophysiology of central vision damage in glaucoma patients with myopia. Hemodynamic changes included systemic assessment of the heart rate variability (HRV) that represents the systemic autonomic regulation. The choroidal vasculature and branches to the ONH are under autonomic regulation and measuring systemic HRV status could represent the control of ocular blood flow to the choroid and the ONH.[16,17] Past studies defined only the vascular incompetence as a reduction of VD from one baseline scan of OCTA, which is limited to represent the continuous nature of blood flow. Additionally, blood pressure instability and fluctuation that leads to unstable blood flow to the optic nerve are important in glaucoma pathogenesis. Therefore, we obtained serial OCTA and evaluated the fluctuation of VD as a dynamic constant, representing the degree of blood flow instability rather than just decreased state of blood flow. Both VD and fluctuation of VD from OCTA were included in this study.

Methods

Subjects

This study followed all guidelines for the investigation of human subjects as required by the Seoul St. Mary's Hospital Institutional Review Board. All subjects were treated in accordance with the tenets of the Declaration of Helsinki. This study included 236 eyes of 140 patients with NTG who visited the Seoul St. Mary's Hospital between January 2015 and December 2020.

The inclusion criteria for patients with NTG with myopia were axial length equal or longer than 24 mm, best-corrected visual acuity ≥20/40, intraocular pressure (IOP) under 21 mm Hg without using hypotensive medications, and without any kind of retinopathy. The presence of hypotension, hypertension, diabetes, migraine, dizziness, cardiovascular disease, and cerebrovascular disease in the subjects were recorded. Participants with history of uncontrolled IOP, uncontrolled hypertension, uncontrolled diabetes, uncontrolled cardiovascular disease, or cerebrovascular disease, terminal glaucoma, and myopia treatment (atropine, progressive addition spectacle lenses, orthokeratology, or multifocal contact lenses) were excluded from the study population.

All the subjects took ophthalmologic tests including best corrected visual acuity, slit-lamp examination, Goldmann applanation tonometry, gonioscopy, automatic refraction, ultrasound pachymetry, axial length biometry (IOLMaster; Carl Zeiss Meditec, Dublin, CA, USA), optic disc photography (Kowa nonmyd WX; Kowa Company Ltd., Tokyo, Japan), retinal nerve fiber layer thickness analysis (Cirrus OCT, version 6.0; Carl Zeiss Meditec), optical coherence tomography angiography (DRI OCT Triton System, Topcon, Tokyo, Japan), and standard automatic perimetry using both 10-2 and 24-2 tests from the Humphrey visual field analyzer (Carl Zeiss Meditec). IOP was measured at every visit and the difference between the lowest and highest IOP was considered as IOP fluctuation in this study. Patients were classified according to their axial length; mild myopia (axial length ≥24 and <26 mm), moderate (≥26 and <28 mm), and severe myopia (≥28 mm).[18,19]

Posterior Scleral Profile

Measurement of optic disc tilt, torsion, disc-foveal angle, and PPA area was done by color disc and red-free retinal nerve fiber layer (RNFL) photographs. All the photographs were taken by two independent examiners (authors K.E.H. and D.Y.S.). Both examiners made sure that the patients placed their chins and foreheads on the head rests of the fundus camera. The subject's eyes were aligned in the right level mark on the forehead support by resetting the chin rest. The patients were told to keep their heads upright during the photograph session and look directly at the internal fixation target of the fundus camera, which was used as a fovea centering marker.[20,21]

Optic disc tilt was defined as the tilt ratio between the longest and shortest diameters of the optic disc. Optic disc torsion was defined as the deviation of the long axis of the optic disc from the perpendicular meridian, and positive angles represent inferotemporal torsion and negative angles represent superotemporal torsion. Disc-foveal angle was defined as the angle between the center of the optic disc and fovea, measured as the angle between the baseline and the horizontal line passing through the center of the disc, as described earlier. Positive values indicate that the fovea is below the optic disc, and negative values indicate that the fovea is superior to the optic disc. The pixel area of the PPA was calculated using ImageJ software, and the pixel area of the optic disc was also calculated. PPA/disc area ratio defined as the ratio between the PPA area and the disc area (PPA/disc ratio = PPA area/disc area).[22–25]

Systemic HRV Assessment

Echocardiography (Cardiotens-01; Meditech Ltd., Budapest, Hungary) and Medicore Heart Rate Analyzer (Model SA-3000P; Medicore, Seoul, Korea) was used in the present study. The Heart Rate Analyzer was developed to assess the status of the autonomic nervous system and balance between sympathetic and parasympathetic system in terms of heart rate.[26–31]

The subjects were controlled to avoid activities that may affect blood pressure at least 2 hours before the test. The echocardiography testing was performed over 5 minutes in controlled conditions by a single experienced technician. Then, the echocardiography signal was transferred to a Medicore Heart Rate Analyzer, which is based on a comprehensive analysis of HRV, systemic hemodynamics, and autonomic regulation.[32]

For assessment of HRV parameters and their subsequent generalization, including other hemodynamic parameters, the standard deviation of normal-normal intervals (SDNNs) index is the mean of all the normal rate-to-rate intervals in echocardiography recording in milliseconds of the standard deviations of all the normal rate-to-rate intervals.[33–35]

Reduced SDNN mainly reflects sympathetic hyperactivity, and increased SDNN reflects parasympathetic hyperactivity.[36] Increased sympathetic activity of the heart results in decreased HRV, which is important in maintaining the

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ability of the heart to respond to various internal and external conditions and may represent systemic vasoconstrictive nature of the patients, including ocular vasculatures.[37,38]

Chorioretinal Vessel Evaluation Using OCTA

The DRI OCT Triton System used a swept source laser with a wavelength of 1050 nm. The angiography is generated by repeated 100,000 times of A-scans per second at the same locations and analyzed from both intensity and phase information, using the Topcon OCTA ratio analysis algorithm. The algorithm for processing the blood flow information is based on Topcon OCTA ratio analysis (OCTARA), which generates en face images via automated layer segmentation around the optic nerve head and macular area into four layers. The four layers are divided by the following standards. The superficial vascular plexus area of macular corresponds to the region starting from 2.5 µm below the internal limiting membrane to 15.5 µm below the junction of the inner plexiform layer (IPL) and inner nuclear layer (INL; IPL/INL). The deep vascular plexus of macular reach from 15.5 µm below IPL/INL to 70 µm below IPL/INL. In the parapapillary region, the radial parapapillary capillary (RPC) segment extending from the internal limiting membrane (ILM) to the RNFL was analyzed for superficial parapapillary vascular plexus. For the imaging of deep parapapillary microvasculature, the embedded segmentation program demarcated the boundary line from 130 µm below the ILM to 390 µm below the basement membrane, including the INL, outer plexiform layer (OPL), outer nuclear layer (ONL), and choroid.[39]

Image processing and VD measurements were performed by scan obtained by size of 4.5 × 4.5 mm and active eye tracking system was applied to remove motional artifacts while achieving images. To calculate macular vascular density VD, ImageJ software (Schneider, C. A., Rasband, W. S., & Eliceiri, K. W. 2012; NIH Image to ImageJ: 25 years of image analysis. Nature Methods, 9(7), 671–675, doi:10.1038/nmeth.2089) was used. Every achieved image underwent 8-bit binarization with ImageJ's built-in algorithm; average threshold grayscale distribution, which automatically calculates with the local average grayscale distribution. Existence of vessel was defined as areas with a score of five or higher. VD was calculated as the ratio of the total vessel area to the total area of the area of interest.

All scans were individually reviewed by two investigators (authors K.E.H. and D.Y.S.) for quality evaluation (i.e. signal strength, segmentation error, loss of fixation, or motion artifact), and substandard scans were excluded. The interobserver reproducibility of measuring parapapillary and macular area choroidal VD was evaluated by having two observers (authors K.E.H. and D.Y.S.). To measure this parameter, 30 randomly selected eyes were checked to confirm the intraclass correlation coefficients and their confidence intervals (CIs).

Corrected Parameters by Ocular Magnification

The effect of ocular magnification was considered and the posterior pole profiles and ONH parameters were corrected according to axial length. The relationship between the measured disc/ RNFL photographs and OCT images diameter (Dm), and the true diameter on the fundus (Dt), can be expressed as: $Dt = p \times q \times Dm$; where $p \times q$ is the overall image magnification factor, p is that of the imaging system, and q is that of the eye. The factor q can be determined: $q = 0.01306 \times (\text{axial length} = 1.82)$. The factor p, omitting any effect arising from image distortion, can be readily calculated from the Bennet formula if the axial length at which Dt = Dm is known (i.e. 23.82 mm here). When Dt = Dm, then $p = 1/q$ and, therefore, $p = 1/[0.01306(23.82–1.82)] = 3.48$.[40]

Definition of VD Fluctuation

This study selected from a group of patients who had received at least more than two OCTAs. Images of the OCTA test performed at the first visit and the OCTA test performed at every follow-up visit were used. OCTA was repeated several times on the day of the visit, because the signal strength of the image may not meet the standard or when it was difficult to read the test result due to artifacts. For each image, VD was calculated as the white pixels divided by the image's total area pixel. Using the VD values obtained from each image, the VD difference between the two images was obtained. Then, with that value, the root mean square (RMS) error was estimated as a measure of variability, defined as VD fluctuation. We used RMS because it is a particular case of the generalized mean with exponent. The RMS of the pairwise differences of the two data sets can serve as a measure how far on average the error is from 0. The mean of the absolute values of the pairwise differences was used as a measure of the variability of the differences.

Definition of Central Scotoma

All subjects underwent SAP using the 24-2 and 10-2 Swedish Interactive Threshold Algorithm (SITA) standard programs with a Humphrey field analyzer II 750i (Carl Zeiss Meditec). A visual field test result was regarded as reliable when fixation loss was <20%, false-positive rate was <15%, and false-negative rate was <15%. Raw 10-2 and 24-2 VF data for all included eyes were extracted. Each VF test point based on 10-2 and 24-2 threshold sensitivity map values. Mean deviation (MD) and pattern standard deviation (PSD) were analyzed. Statistical analysis was performed by selecting each part of the quadrant based on the most central point on the visual field test results. Twelve central VF points within the 10 degrees region of the 24-2 test and 68 VF points of the 10-2 test were used for analysis.[41,42]

Initially to define subjects with central visual field defect (CVFD), we analyzed the initial consecutive SITA 24-2 results. CVFD was defined as VF defects within the central 10 degrees on the pattern deviation probability map with clusters of 3 points with a probability of less than 5%, or 2 or more test points with a probability of less than 1% or smaller. All subjects had VF defects located within the superior or inferior hemifield of the central 10 degrees regardless of the presence of defects outside the central 10 degrees. Visual function within the central 10 degree region was evaluated by calculating the retinal sensitivity of the central 12 points of the SITA 24-2 test and the MD and PSD of the 10-2 VF tests. Central retinal sensitivity was calculated by converting logarithmic dB scale to nonlogarithmic scale using the formula [dB scale = 10 log(1/Lambert)] in the central 12 points of SITA 24-2.

Statistical Analysis

We used the Student's *t*-test to compare continuous variables and the $\chi 2$ test to compare categorical variables between

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patients with mild and moderate to severe myopic glaucoma groups by axial length. Possible associations between the structural and vascular variables (including posterior scleral factors, autonomic dysfunction, and parapapillary choroidal VD) and visual functional parameters were analyzed by calculating Pearson correlations. Correlation coefficient from the Pearson correlation analysis was graded using the guideline by Evans: 0 to 0.19 as very weak, 0.20 to 0.39 as weak, 0.40 to 0.59 as moderate, 0.60 to 0.79 as strong, and 0.80 to 1.00 as very strong correlation.[43]

Binary logistic regression analyses were used to identify structural and vascular variables associated with the presence of the central scotoma. Linear regression analysis with the dependent variable being the retinal sensitivity of the central 12 points of 24-2 VF test was performed. The independent variables were posterior scleral factors, parameters of autonomic dysfunction, and parameters of parapapillary choroidal VD.

Independent variables yielding $P < 0.10$ in the univariate model were included in the multivariate model. When the P value is set to 0.05, the items included as variables are judged to be inappropriate, so model selection was guided by 21 backward stepwise elimination conducted on the model containing all variables with $P < 0.10$ in the univariable analysis.[44]

All P values were from 2-sided tests and results were deemed statistically significant at $P < 0.05$. All statistical analyses were performed with SPSS for Windows statistical software, version 16.0 (SPSS Inc.).

Results

The baseline characteristics of the 236 subjects are summarized in Table 1. The mean ± standard deviation of age was 53.14 (±13.78) years. Initial IOP and long-term IOP fluctuation were 16.49 (±5.35) mm Hg and 3.29 (±4.17) mm Hg, respectively. Axial length and spherical equivalent were 26.35 (±1.64) mm (range = 24.00–30.00 mm) and −2.5746 (±3.65) diopters, respectively. According to SITA 24-2, 79 subjects had initial central scotoma.

Correlation between structural characteristic of myopia and other variables are summarized in Table 2. Axial length, spherical equivalent, and posterior scleral profiles (disc-foveal angle, disc torsion, disc tilt ratio, and PPA/disc area ratio) were checked for correlation. Lower superficial and deep VD in the peripapillary region showed significant correlation with longer axial length ($P = 0.017$ and $P = 0.011$) and greater PPA/disc area ratio ($P = 0.047$ and $P = 0.035$). Lower macular deep VD also showed significant correlation with longer axial length ($P = 0.009$). Smaller fluctuation of macular deep VD showed significant correlation with longer axial length, greater disc tilt ratio, and greater PPA/disc area ratio ($P = 0.022$, $P = 0.024$, and $P = 0.044$). Comparison between patients with glaucoma with mild and moderate to severe myopia are summarized in Table 3. The moderate to severe myopia group showed significantly lower initial deep VD in the peripapillary and macular area compared to the mild myopia group. Additionally, the moderate to severe myopia group showed significantly greater deep VD fluctuation in the macular area compared to the mild myopia group. We further classified the patients into three groups to check the tendency of VD and fluctuation of VD according to the degree of myopia. As the degree of myopia gets greater, the initial deep VD decreases in the peripapillary and macular area (Fig. 1A). The peripapillary deep VD was significantly lower in the severe myopic group compared to the mild ($P = 0.023$) and moderate myopia group ($P = 0.001$). However, the fluctuation of deep VD gets greater as the degree of myopia gets greater in both the absolute value (Fig. 1B) and the percentage value of the deep VD (Fig. 1C). Superficial VD fluctuation was significantly lower in the severe myopia group compared to the mild and moderate myopia group, however, deep VD fluctuation was significantly greater in the severe myopia group compared to the mild ($P < 0.001$) and moderate myopia group ($P < 0.001$). To summarize, total deep VD decreases as the degree of myopia increases and shows correlation with the posterior pole profiled related to myopia. However, the fluctuation of VD has a tendency to get greater as the degree of myopia increases.

Correlation between parameters of the VF and other variables are summarized in Table 4. MD, PSD, mean retinal sensitivity value of the central 12 points of SITA 24-2 test and MD and PSD of SITA 10-2 test were evaluated.

Table 1. Demographic and Ocular Characteristics of Study Subjects

	Total $n = 236$
Age, y	53.14 (±13.78)
Sex, male:female	96:140
Hypertension, *n* (%)	44 (18.6%)
Diabetes, *n* (%)	14 (5.9%)
Disc hemorrhage, *n* (%)	93 (39.4%)
Follow up duration, days	201.64 (±20.09)
Best corrected visual acuity, decimal	0.8081 (±0. 25)
Initial intraocular pressure, mm Hg	16.49 (±5.35)
IOP fluctuation, mm Hg	3.29 (±4.17)
Axial length, mm	26.35 (±1.64)
Central corneal thickness, µm	532.30 (±45.05)
Spherical equivalent, diopters	−2.5746 (±3.65)
Disc-foveal angle, degree	6.51717 (±3.24)
Disc torsion, degree	0.526 (±17.84)
Disc tilt ratio	1.19 (±0.15)
Peripapillary atrophy per disc area ratio	0.51 (±0. 55)
The standard deviation of the mean of qualified normal-to-normal intervals of heart rate variability, ms	40.88 (±28.44)
Initial peripapillary area superficial VD, %	52.18 (±13.46)
Initial peripapillary area deep VD, %	49.12 (±4.74)
Initial macula area deep VD, %	48.71 (±3.93)
Peripapillary area superficial VD fluctuation, %	3.71 (±4.91)
Peripapillary area deep VD fluctuation, %	3.97 (±3.18)
Macula area deep VD fluctuation, %	2.53 (±2.64)
MD in SITA 24-2, dB	−4.15 (±5.60)
PSD in SITA 24-2, dB	4.87 (±3.80)
MD in SITA 10-2, dB	−5.72 (±6.17)
PSD in SITA 10-2, dB	5.59 (±3.43)
Central 12-point MD sum in SITA 24-2, dB	−41.06 (±43.79)
Central scotoma presence in SITA 24-2, *n* (%)	79 (33.5%)
Central scotoma progression in SITA 24-2, *n* (%)	36 (15.3%)
RNFL average thickness, µm	78.39 (±14.31)
GCA average thickness, µm	69.90 (±9.36)

IOP, intraocular pressure; PPA, peripapillary atrophy; HRV, heart rate variability; LF, low frequency of HRV; HF, high frequency of HRV; LF/HF, ratio of LF and HF; VD, vessel density; SITA, Swedish Interactive Threshold Algorithm; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; GCA, ganglion cell analysis.

Data are means (±SD) or numbers (%), as appropriate.

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Table 2. Correlation Between Structural Characteristic of Patients With Myopia and Glaucoma Variables

		Axial Length, mm	Spherical Equivalent, Diopters	Disc-Foveal Angle, Degree	Disc Torsion, Degree	Disc Tilt Ratio	PPA Per Disc Area Ratio
Age, y	r	−0.408**	0.263**	−0.123	0.010	−0.047	−0.163*
	P	0.000	0.000	0.059	0.910	0.471	0.012
Best corrected visual acuity, decimal	r	−0.009	0.054	0.143*	−0.222*	−0.171**	0.016
	P	0.896	0.409	0.028	0.014	0.009	0.807
Initial intraocular pressure, mmHg	r	0.078	−0.046	−0.037	−0.007	−0.084	−0.036
	P	0.235	0.481	0.571	0.942	0.197	0.586
IOP fluctuation, mmHg	r	0.098	0.003	−0.084	−0.069	−0.047	−0.079
	P	0.135	0.965	0.201	0.448	0.474	0.225
Central corneal thickness, µm	r	−0.080	−0.123	−0.009	0.045	−0.003	−0.096
	P	0.221	0.059	0.887	0.619	0.969	0.143
Initial peripapillary area superficial VD, %	r	−0.128**	−0.131	−0.047	0.076	0.000	−0.004*
	P	0.017	0.068	0.481	0.617	0.913	0.047
Initial peripapillary area deep VD, %	r	−0.208**	−0.148*	−0.003	−0.172	−0.004	−0.022*
	P	0.011	0.032	0.962	0.070	0.950	0.035
Initial macula area deep VD, %	r	−0.153**	0.121*	0.053	−0.065	0.006	0.061
	P	0.009	0.043	0.538	0.581	0.922	0.379
Peripapillary area superficial VD fluctuation, %	r	−0.160*	−0.090	−0.050	−0.054	−0.058	−0.006
	P	0.020	0.192	0.472	0.572	0.399	0.935
Peripapillary area deep VD fluctuation, %	r	0.132	−0.086	−0.087	−0.041	0.013	−0.027
	P	0.093	0.291	0.187	0.708	0.867	0.736
Macula area deep VD fluctuation, %	r	−0.072*	0.029	−0.097	0.079	−0.033*	−0.010*
	P	0.022	0.457	0.231	0.399	0.024	0.044
RNFL average thickness, µm	r	−0.038	−0.007	0.103	−0.135	−0.100	−0.036
	P	0.582	0.917	0.135	0.159	0.150	0.607
GCA average thickness, µm	r	−0.123	0.138	0.069	0.126	−0.053	−0.075
	P	0.177	0.131	0.450	0.167	0.559	0.411

Correlation coefficient (r) and *P* value analyzed by Pearson's correlation analysis.
* Significant at 0.05 level (2-tailed).
** Significant at 0.01 level (2-tailed).
IOP, intraocular pressure; PPA, peripapillary atrophy; HRV, heart rate variability; LF, low frequency of HRV; HF, high frequency of HRV; LF/HF, ratio of LF and HF; VD, vessel density; SITA, Swedish Interactive Threshold Algorithm; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

Longer axial length showed significant negative correlation with MD of SITA 10-2 test ($P = 0.004$). Worse mean retinal sensitivity of the central 12 points of SITA 24-2 test showed significant correlation with greater disc-foveal angle, greater disc tilt ratio, and larger PPA/disc area ratio ($P = 0.018$, $P = 0.011$, and $P = 0.038$). MD of SITA 10-2 test showed significant negative correlation with axial length, disc torsion degree, and PPA/disc area ratio. Lower macular deep VD, lower deep VD fluctuation in the peripapillary area, and lower macular deep VD fluctuation were significantly correlated to central 12 points value of SITA 24-2 ($P = 0.009$, $P = 0.006$, and $P = 0.047$). These results indicate that both myopic factors and VD parameters including VD fluctuation show correlation with the central VF function.

We divided 79 subjects with initial central scotoma according to their MD values of the SITA 10-2 test (Table 5). Mild central scotoma was defined as subjects with MD value better than –5dB on SITA 10-2 test. Moderate to severe central scotoma was defined as subjects with worse MD value than –5dB on SITA 10-2 test. Moderate to severe central scotoma group showed marginal statistical significance in terms of greater disc tilt ratio, smaller disc-foveal angle, and lower macular VD than the mild central scotoma group ($P = 0.061$, $P = 0.059$, and $P = 0.051$, respectively). Moderate to severe central scotoma group showed significantly longer axial length, lower SDNN of HRV, and greater VD fluctuation in both peripapillary and macular area than the mild central scotoma group ($P = 0.032$, $P = 0.039$, $P = 0.001$, and $P = 0.006$, respectively). These results show that myopic parameters, systemic autonomic parameters, and VD parameters on OCTA, especially VD fluctuation, related to the presence of central scotoma in patients with myopic glaucoma.

Logistic regression analysis of the presence of central scotoma in patients with myopic glaucoma are summarized in Table 6. Univariate and multivariate analysis were performed to find out the reduced SDNN of the HRV, lower macular deep VD, and greater deep VD fluctuation in the peripapillary area were significantly related to the presence of central scotoma in patients with myopic glaucoma ($P = 0.011$, $P = 0.001$, and $P = 0.005$, respectively).

Linear regression analysis using the center 12 points from SITA 24-2 test as the dependent variable are summarized in Table 7. Only deep VD fluctuation in the peripapillary area showed significant association with the sensitivity of the center 12 points from SITA 24-2 test ($P = 0.012$).

Three representative cases are shown in Figure 2. Each of the subjects represents that fluctuation of the macular VD and peripapillary VD are related to the degree of the central VF defect in patients with myopic glaucoma. In addition to the three representative cases, there is a diagram showing that the correlation between macular VD and peripapillary VD are related to the degree of the central VF defect.

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Table 3. Comparisons Between Patients With Mild and Moderate to Severe Myopic Glaucoma

Variable	Mild Myopia (n = 114)	Moderate to Severe Myopia (n = 122)	P Value
Age, y	58.19 (±12.04)	48.41(±13.66)	0.000*
Sex, female, n (%)	65 (57.0%)	75 (61.5%)	0.486**
Hypertension, n (%)	29 (25.4%)	15 (12.3%)	0.010**
Diabetes, n (%)	4 (3.5%)	10 (8.2%)	0.128**
Disc hemorrhage, n (%)	45 (39.5%)	48 (39.3%)	0.984**
Follow up duration, days	191.25 (±20.97)	211.35 (±20.42)	0.457*
Best corrected visual acuity, decimal	0.79 (±0.26)	0.82 (±0.23)	0.337*
Initial intraocular pressure, mm Hg	16.57 (±5.24)	16.42 (±5.469)	0.827*
IOP fluctuation, mm Hg	3.56 (±4.53)	3.09 (±3.88)	0.423*
Central corneal thickness, µm	538.32 (±39.57)	526.66 (±49.12)	0.047*
Spherical equivalent, diopters	−0.88 (±2.02)	−4.14 (±4.10)	0.000*
Disc-foveal angle, degree	6.93 (±3.20)	6.12 (±3.25)	0.054*
Disc torsion, degree	0.524 (±18.78)	0.565 (±17.08)	0.067*
Disc tilt ratio	1.16 (±0.11)	1.23 (±0.17)	0.000*
Peripapillary atrophy per disc area ratio	0.28 (±0.27)	0.72 (±0.66)	0.000*
The standard deviation of the mean of qualified normal-to-normal intervals of heart rate variability, ms	41.20 (±31.00)	40.55 (±25.75)	0.902*
Initial peripapillary area superficial VD, %	48.71 (±14.25)	52.59 (±14.03)	0.031*
Initial peripapillary area deep VD, %	50.08 (±5.13)	48.71 (±6.08)	0.015*
Initial macula area deep VD, %	49.27 (±5.49)	48.15 (±3.38)	0.043*
Peripapillary area superficial VD fluctuation, %	4.17 (±5.84)	3.11 (±3.73)	0.419*
Peripapillary area deep VD fluctuation, %	3.18 (±4.15)	3.64 (±3.59)	0.071*
Macula area deep VD fluctuation, %	2.51 (±3.86)	2.48 (±1.20)	0.031*
MD in SITA 24-2, dB	−4.13 (±6.47)	−4.17 (±4.89)	0.964*
PSD in SITA 24-2, dB	4.53 (±2.18)	4.89 (±3.31)	0.746*
MD in SITA 10-2, dB	−4.13268 (±5.71)	−5.17986 (±6.50)	0.340*
PSD in SITA 10-2, dB	3.9170 (±2.89)	5.1124 (±3.72)	0.142*
Central 12-point MD sum in SITA 24-2, dB	−36.0326 (±37.39)	−44.8607 (±47.86)	0.145*
Central scotoma presence in SITA 24-2, n (%)	34 (37.0%)	45 (36.99%)	0.991**
RNFL average thickness, µm	78.56 (±14.67)	78.26 (±14.11)	0.882*
GCA average thickness, µm	70.21 (±9.46)	69.54 (±9.32)	0.694*

IOP, intraocular pressure; PPA, peripapillary atrophy; HRV, heart rate variability; LF, low frequency of HRV; HF, high frequency of HRV; LF/HF, ratio of LF and HF; VD, vessel density; SITA, Swedish Interactive Threshold Algorithm; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; GCA, ganglion cell analysis.

Data are means (±SD) or numbers (%), as appropriate. Independent Student's t-test and Chi-square test were used.

* t Test.

** χ^2 Test.

Discussion

This study investigated related factors to central VF damage observed in glaucoma patients with myopia. Both structural changes by myopia and hemodynamic factors in terms of SDNN of the HRV test and VD parameters of OCTA were related to the central VF function in patients with myopic glaucoma. PPA/disc area ratio, axial length, disc tilt, disc torsion, and disc-foveal angle had significant correlation with central VF parameters. Additionally, myopic changes itself reduced the VD parameters, including VD fluctuation. However, the association with the presence of central scotoma or values of the retinal sensitivity in the central 10-degree region of the VF showed consistent relationship with deep VD fluctuation in the peripapillary area in patients with myopic glaucoma in this study. This suggest that although blood flow is reduced due to myopic changes around the ONH, fluctuation of the blood flow is an important factor to the involvement of central VF function in patients with myopic glaucoma.

Several studies have explored the structural changes in the eyeball that are frequently observed in myopia. For example, structural changes of myopia can be characterized using the posterior scleral profiles.[4,45] Myopia by itself causes scleral deformation, leading to damage to the optic nerve.[46] Additionally, according to Yang et al., there was a tendency of reduced VD in myopic eyes, and, in particular, axial length was significantly associated with a decrease in VD in the macular region.[47] This means myopic changes not only adds structural damages, but also impairs vascular status of the retinal ganglion cells that may influence glaucoma. In our study, we confirmed that there was a significant difference in peripapillary and macular VD in severe myopia. Additionally, VD fluctuation was analyzed in addition to VD.

We decided not to simply use the absolute fluctuation value when analyzing the VD fluctuation. Instead, we decided to set the initial VD result as the denominator to analyze the relative value of fluctuation. This is because the initial VD is set lower in the case of highly myopic eyes than in mildly myopic eyes, as shown in first row of Figure 1. The second row of Figure 1 shows the result of comparative analysis of the absolute value of VD fluctuation. In the case of VD fluctuation in the deep area, there is no significant difference between mild and moderate myopia groups. In addition, in the case of VD fluctuation in the

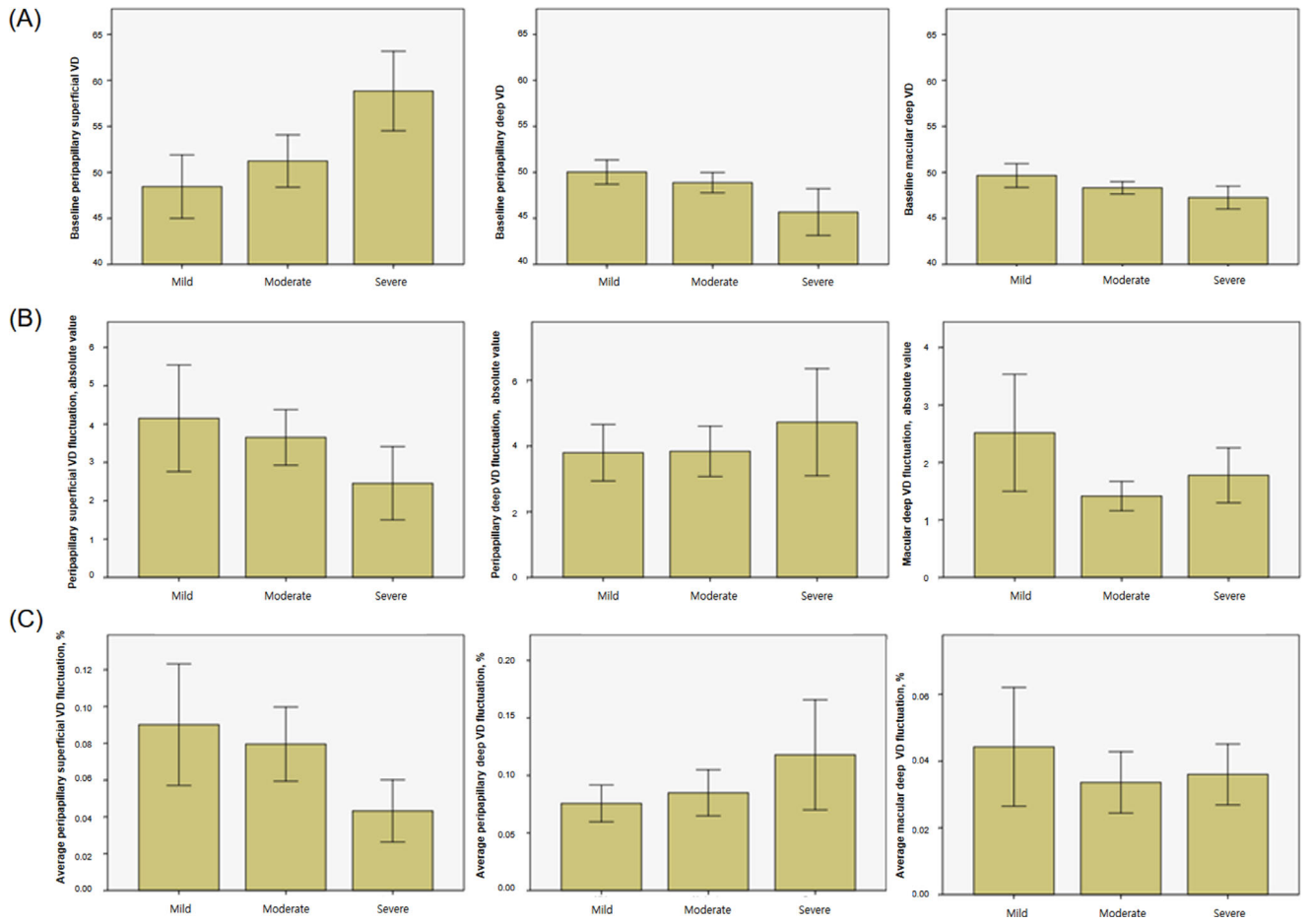

Figure 1. Comparison of baseline vessel density and vascular fluctuation in each area according to the degree of myopia. Each image represents the results of three groups of myopia. As the degree of myopia gets greater, initial deep VD decreases in the peripapillary and macular area (**A**). However, the fluctuation of deep VD gets greater as the degree of myopia gets greater in absolute values (**B**) and percentage values (**C**).

macular area, the difference between each group is confirmed, but the tendency according to the degree of myopia is not confirmed. As mentioned earlier, we assumed that the relative value of fluctuation reflecting the initial VD value related to the difference in the degree of myopia is more accurate in this comparison of VD fluctuations. At the third row of Figure 1, the results using the relative VD fluctuation values with the initial VD value set as the denominator and the absolute value of the VD fluctuation set as the numerator. Even though there was no significant difference in the absolute value of VD fluctuation in the deep peripapillary and macular area, the percentage value relative to the initial VD showed significant difference between myopic groups. This may indicate that VD fluctuation relative to the initial VD value is important since initial VD value may decrease as the degree of myopia gets greater.

It is assumed that the decrease in VD fluctuation is due to the decrease in retinal thickness owing to the elongation of axial length. According to Wang et al., structural changes in the optic nerve and decreased circulation of micro-blood flow accelerated the progression of VF damage.[48] According to Shin et al., in patients with moderate-to-advanced glaucoma, the correlation between vasculature and function was stronger in the macular region than the peripapillary region.[49] According to Fujino et al., damage to the central VF is reflected by structural damage to the optic nerve.[50] In our study, when we compared the structural deformation and decreased blood flow in relation to the presence of central VF damage in the regression analysis, the decrease in blood flow was a greater associated factor. Therefore, it is assumed that the decrease in blood flow has a significantly greater effect on central vision damage than structural damage when myopia is present.

Studies have also reported that hemodynamic factors are associated with glaucoma progression.[11,51] In patients with glaucoma with controlled IOP, hemodynamic factors have been studied by dividing them into systemic and local risk factors. Examples include HRV, which is commonly used to assess systemic hemodynamic status, and OCTA to assess the local hemodynamic status of the eye.[52,53] According to Shin et al., structural changes, such as peripapillary scleral deformation, are commonly observed in myopia, affecting hemodynamic status around the ONH and confirming the results of microvascular dropout.[54] According to Li et al., these structural changes in myopia can be expected to accompany hemodynamic changes.[55] This study investigated whether hemodynamic changes could explain central VF damage in

Table 4. Correlation Between Visual Function and Patients with Myopic Glaucoma Variables

		SITA 24-2			SITA 10-2	
		MD, dB	PSD, dB	Central 12-point MD, dB	MD, dB	PSD, dB
Axial length, mm	*r*	−0.076	0.005	−0.105	−0.233**	0.127
	P	0.137	0.470	0.063	0.004	0.075
Central corneal thickness, µm	*r*	0.037	0.154*	0.068	−0.071	−0.078
	P	0.299	0.012	0.160	0.210	0.190
Spherical equivalent, diopters,	*r*	0.071	0.040	−0.003	−0.003	−0.023
	P	0.150	0.284	0.485	0.487	0.399
Disc-foveal angle, degree	*r*	−0.084	0.062	−0.081*	0.024	0.042
	P	0.111	0.185	0.018	0.394	0.316
Disc torsion degree	*r*	−0.118	0.277	−0.078	−0.302*	0.147
	P	0.215	0.652	0.414	0.012	0.231
Disc tilt ratio	*r*	−0.064	0.042	−0.150*	−0.036	0.080
	P	0.179	0.271	0.011	0.344	0.181
Peripapillary atrophy per disc area ratio	*r*	−0.177**	0.090	−0.117*	−0.443**	0.046
	P	0.005	0.096	0.038	0.000	0.301
The standard deviation of the mean of qualified normal-to-normal intervals of heart rate variability, ms	*r*	−0.034	0.001	−0.037	0.105	0.022
	P	0.374	0.497	0.361	0.133	0.426
Initial peripapillary area superficial VD, %	*r*	0.246**	−0.311**	0.049	0.037	−0.073
	P	0.001	0.001	0.251	0.403	0.203
Initial peripapillary area deep VD, %	*r*	0.094	−0.124*	−0.067	0.053	0.078
	P	0.075	0.037	0.185	0.289	0.199
Initial macula area deep VD, %	*r*	0.226**	−0.120*	0.156**	−0.071	0.041
	P	0.001	0.043	0.009	0.199	0.317
Peripapillary area superficial VD fluctuation, %	*r*	−0.122*	0.284**	−0.037	−0.075	−0.073
	P	0.039	0.001	0.297	0.198	0.203
Peripapillary area deep VD fluctuation, %	*R*	−0.053	0.063	−0.177**	−0.154*	0.014
	P	0.231	0.181	0.006	0.042	0.431
Macula area deep VD fluctuation, %	*r*	−0.017	0.034	−0.115	−0.052	0.182
	P	0.409	0.315	0.047	0.284	0.017
RNFL average thickness, µm	*r*	0.575**	−0.248**	0.436**	0.484**	−0.410**
	P	0.000	0.000	0.000	0.000	0.000
GCA average thickness, µm	*r*	−0.047*	0.045	−0.187*	−0.005*	0.123
	P	0.043	0.139	0.039	0.048	0.119

Correlation coefficient (r) and *P* value analyzed by Pearson's correlation analysis.
* Significant at 0.05 level (2-tailed).
** Significant at 0.01 level (2-tailed).
IOP, intraocular pressure; PPA, peripapillary atrophy; HRV, heart rate variability; LF, low frequency of HRV; HF, high frequency of HRV; LF/HF, ratio of LF and HF; VD, vessel density; SITA, Swedish Interactive Threshold Algorithm; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

myopia. We speculated that among the variables that represent structural changes in myopia, there may be factors that have a relatively strong influence on hemodynamic factors. Additionally, we decided to analyze the VD considering it not to be a fixed value, but a value that may fluctuate. On further analysis, we found that the VD fluctuation of the macular area significantly correlated with disc tilt ratio in addition to the axial length and PPA ratios ($P = 0.021$, $P = 0.025$, and $P = 0.046$, respectively). According to Wierzbowska et al. and Park et al., the HRV was found to be low when considering the progression of central vision in patients with normal-tension glaucoma, and those with autonomic dysfunction, such as migraine and orthostatic hypotension, where it was associated with rapid progression of the injury.[56,57] In our study, the difference in VD in the peripapillary and macular area was not significant between the two groups with different degrees of central VF damage. In contrast, the fluctuation of VD in the peripapillary and macular area was significantly greater in the group with severe central VF damage ($P = 0.001$ and $P = 0.005$). Patients with abnormal HRV and autonomic dysfunction have features, such as low systemic blood pressure and fluctuating blood pressure. We think instability of the systemic blood pressure due to autonomic dysfunction could be related to VD fluctuation and blood flow instability to the ONH may contribute to the central VF damage. Therefore, both local and systemic hemodynamic status could affect the central VF function in patients with myopic glaucoma.

Both structural and hemodynamic changes by myopia seems to influence the central VF function in myopic eyes. Structural changes and damage to central vision in myopic eyes are consistent with previous studies. Similarly, in this study, the degree of myopia was found to be an important factor when comparing the two groups divided according to the degree of damage to the central VF. According to Moghadas et al., the decreased sensitivity of the VF examination in high myopia was related to the decrease in the thickness of the retinal layer.[58] Decrease in the thickness of the ganglion cell layer could be caused by stretching of the retina, and Wolsley et al. explained that this reduction in thickness can be mainly divided into photoreceptor cells and the inner layer of the retina.[59] It is also confirmed

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Table 5. Comparisons Between Patients With Mild and Moderate to Severe Central Scotoma Glaucoma

Variable	Mild Central Scotoma (n = 58)	Moderate to Severe Central Scotoma (n = 21)	P Value
Age, y	55.23 (±16.28)	58.00 (±12.42)	0.569*
Sex, female, n (%)	32 (55.17%)	14 (66.67%)	0.273**
Hypertension, n (%)	7 (12.06%)	9 (42.85%)	0.129**
Diabetes, n (%)	2 (3.44%)	1 (4.76%)	0.754**
Disc hemorrhage, n (%)	20 (34.48%)	11 (52.38%)	0.061**
Follow up duration, days	200.74 (±15.77)	211.35 (±20.42)	0.384*
Best corrected visual acuity, decimal	0.81 (±0.27)	0.75 (±0.25)	0.501*
Initial intraocular pressure, mm Hg	3.15 (±2.51)	2.75 (±2.27)	0.600*
IOP fluctuation, mm Hg	15.29 (±3.49)	16.02 (±5.03)	0.927*
Central corneal thickness, µm	538.46 (±50.61)	524.50 (±99.50)	0.455*
Axial length, mm	24.89 (±6.98)	25.02 (±6.05)	0. 032*
Spherical equivalent, diopters	−0.97(±1.34)	−2.71 (±3.47)	0.142*
Disc-foveal angle, degree	6.27 (±3.20)	5.89 (±3.25)	0.061*
Disc torsion, degree	0.531 (±11.47)	0.593 (±13.15)	0.104*
Disc tilt ratio	1.03 (±0.27)	1.57 (±0.34)	0.059*
Peripapillary atrophy per disc area ratio	0.38 (±0.27)	0.72 (±0.66)	0.172*
The standard deviation of the mean of qualified normal-to-normal intervals of heart rate variability, ms	40.97 (±20.38)	35.31 (±32.15)	0.039*
Initial peripapillary area superficial VD, %	36.71 (±5.21)	34.87 (±5.19)	0.255*
Initial peripapillary area deep VD, %	53.23 (±4.76)	52.57 (±3.88)	0.828*
Initial macula area deep VD, %	54.84 (±2.32)	51.56 (±2.45)	0.051*
Peripapillary area superficial VD fluctuation, %	3.44 (±3.86)	3.11 (±4.36)	0.809*
Peripapillary area deep VD fluctuation, %	2.96 (±2.55)	4.97 (±2.02)	0.001*
Macula area deep VD fluctuation, %	2.27 (±0.83)	2.62 (±0.62)	0.005*
RNFL average thickness, µm	78.68 (±13.28)	77.10 (±10.72)	0.754*
GCA average thickness, µm	71.42 (±9.46)	68.19 (±8.15)	0.194*

IOP, intraocular pressure; PPA, peripapillary atrophy; HRV, heart rate variability; LF, low frequency of HRV; HF, high frequency of HRV; LF/HF, ratio of LF and HF; VD, vessel density; SITA, Swedish Interactive Threshold Algorithm; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; GCA, ganglion cell analysis.

Data are means (±SD) or numbers (%), as appropriate. Independent Student's t-test and Chi-square test were used.

* t Test.

** χ^2 Test.

Table 6. Univariate and Multivariate Logistic Regression Analysis of Central Scotoma Presence in Patients With Glaucoma

	Univariate		Multivariate	
	ß (95% CI)	P Value	ß (95% CI)	P Value
Age, y	0.968 (0.791 to 1.206)	0.671		
Initial intraocular pressure, mm Hg	0.918 (0.618 to 1.417)	0.738		
IOP fluctuation, mm Hg	0.211 (0.038 to 1.155)	0.073	0.647 (0.381 to 1.100)	0.108
Axial length, mm	5.093 (0.738 to 35.163)	0.099	1.711 (0.820 to 3.568)	0.152
Central corneal thickness, µm	0.989 (0.968 to 1.036)	0.510		
Spherical equivalent, diopters	0.744 (0.409 to 1.352)	0.240		
Disc-foveal angle, degree	0.747 (0.389 to 1.073)	0.339		
Disc torsion degree	1.014 (0.808 to 3.154)	0.726		
Disc tilt ratio	1.018 (1.000 to 53.033)	0.083	1.044 (0.008 to 38.585)	0.180
Peripapillary atrophy per disc area ratio	1.531 (1.001 to 1.334)	0.045	1.070 (0.003 to 1.711)	0.103
The standard deviation of the mean of qualified normal-to-normal intervals of Heart Rate Variability, ms	0.961 (0.811 to 1.027)	0.057	0.924 (0.855 to 0.992)	0.011
Initial peripapillary area superficial VD, %	0.969 (0.807 to 1.284)	0.543		
Initial peripapillary area deep VD, %	0.917 (0.302 to 1.896)	0.955		
Initial macula area deep VD, %	0.927 (0.853 to .997)	0.048	0.845 (0.756 to 0.931)	0.001
Peripapillary area superficial VD fluctuation, %	1.187 (0.394 to 1.208)	0.221		
Peripapillary area deep VD fluctuation, %	2.419 (1.007 to 5.733)	0.018	1.517 (1.131 to 2.039)	0.005
Macula area deep VD fluctuation, %	1.229 (0.379 to 1.809)	0.643		

CI, confidence interval; IOP, intraocular pressure; PPA, peripapillary atrophy; HRV, heart rate variability; VD, vessel density; SITA, Swedish Interactive Threshold Algorithm; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

Multivariate regression analysis included factors of P values lower than 0.1 in univariate analysis.

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Table 7. Univariate and Multivariate Linear Regression Analysis of Center 12 Points MD From SITA 24-2 in Patients With Glaucoma

	Univariate		Multivariate	
	ß (95% CI)	*P* Value	ß (95% CI)	*P* Value
Age, y	0.121 (−1.518 to 1.537)	0.582		
Initial intraocular pressure, mm Hg	−0.231 (−2.772 to 3.274)	0.447		
IOP fluctuation, mm Hg	−0.104 (−3.568 to 4.087)	0.741		
Axial length, mm	−0.517 (−7.323 to −0.409)	0.009	−0.063 (−6.853 to 2.930)	0.430
Central corneal thickness, µm	0.047 (0.009 to 0.105)	0.039	0.055 (−0.211 to 1.089)	0.424
Spherical equivalent, diopters	−0.018 (−6.348 to 1.224)	0.936		
Disc-foveal angle, degree	−0.068 (−4.019 to 4.217)	0.705		
Disc torsion degree	−0.013 (−1.859 to 6.444)	0.941		
Disc tilt ratio	−0.144 (−13.194 to 4.216)	0.905		
Peripapillary atrophy per disc area ratio	−0.365 (−9.763 to −0.182)	0.018	−0.089 (−21.634 to 5.796)	0.256
The standard deviation of the mean of qualified normal-to-normal intervals of heart rate variability, ms	−0.009 (−1.055 to 1.023)	0.144		
Initial peripapillary area superficial VD, %	0.162 (−1.512 to 0.951)	0.377		
Initial peripapillary area deep VD, %	0.296 (−3.109 to 1.409)	0.166		
Initial macula area deep VD, %	0.384 (0.169 to 1.020)	0.016	0.125 (−3.065 to 0.143)	0.056
Peripapillary area superficial VD fluctuation, %	−0.103 (−5.034 to 1.751)	0.341		
Peripapillary area deep VD fluctuation, %	−0.267 (−6.588 to −0.048)	0.031	−0.173 (−3.968 to −0.049)	0.012
Macula area deep VD fluctuation, %	−0.048 (−4.568 to 6.659)	0.718		

IOP, intraocular pressure; PPA, peripapillary atrophy; HRV, heart rate variability; LF, low frequency of HRV; HF, high frequency of HRV; LF/HF, ratio of LF and HF; VD, vessel density; SITA, Swedish Interactive Threshold Algorithm; MD, mean deviation; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

Multivariate regression analysis included factors of *P* values lower than 0.1 in univariate analysis.

that there is variation in macular thickness in patients with myopia, and such foveal depression and photoreceptor outer segment elongation may lead to decreased visual function.[60,61] Degeneration of the PPA area is one of the most common findings in myopia along with disc tilt.[62,63] The direction and degree of peripapillary tilt in high myopia was significantly correlated with central VF damage.[64] Damage to the lamina cribrosa was also associated with optic disc tilt, which may explain why the location of VF damage is within the central VF region in myopic eyes.[65] In addition to structural deformation associated with myopia, other factors, such as impaired blood flow, could be in accordance with central scotoma in myopic eyes. A typical example of this is microvascular dropout which is frequently reported in former studies. Impaired blood flow factor is also shown by analysis of radial peripapillary capillary and deep parafoveal vessel density showed a decrease in retinal perfusion in myopic eyes.[66] In glaucoma patients with myopia, the subfoveal choroidal blood velocity, volume, and flow parameters were decreased, which is thought to be a factor influencing glaucoma optic nerve damage.[67] What sets this study apart from previous studies is that we investigated the association between central VF impairment and hemodynamic impairment in myopia. In general, glaucoma optic nerve changes result in peripheral VF damage, which is explained by the mechanical origin. In addition to the structural changes in myopia that cause mechanical damage to lamina cribrosa, which are explained similarly to the mechanism of optic nerve changes in general glaucoma, hemodynamic impairment characteristic of myopia was suspected as the cause of damage to the central VF region. Especially, blood flow instability measured by VD fluctuation was an important factor associated with the presence of central scotoma in myopic glaucomatous eyes. Both systemic hemodynamic factors and myopic structural changes could give rise to the VD fluctuation in myopic eyes.

The limitation of this study is that we performed the OCTA test used to determine the hemodynamic relationship of patients with glaucoma with central vision injury and myopia discontinuously. If we performed the two tests at close intervals, we could investigate the effect of VD fluctuation on OCTA, which identifies the hemodynamic relationship, in more detail. In addition, due to the structural deformation of the posterior sclera accompanied with myopia, OCTA signal deterioration and artifacts were inevitable, and we selected the result according to the signal quality. In the case of unclear test results in OCTA, a reduction in the number of samples was inevitable, considering the subject to be excluded. Additionally, there was no evidence that the vascular instability found on OCTA directly affected the central scotoma. However, as mentioned in previous studies, we believe that systemic and local vascular instability can provide useful information for predicting glaucoma-related optic nerve damage. Last, there is a limitation for the issue of magnification and that measured VD may vary between subjects and groups. Effect of ocular magnification was considered, so we calculated all the achieved data from the Bennet formula. But still, the scanned area that we used to measure VD would vary among individuals according to the degree of myopia which needs caution when interpreting our findings.

Conclusion

In summary, central VF defects had a significant relationship not only with the structural change of the characteristics of myopia but also with a decrease in blood flow in

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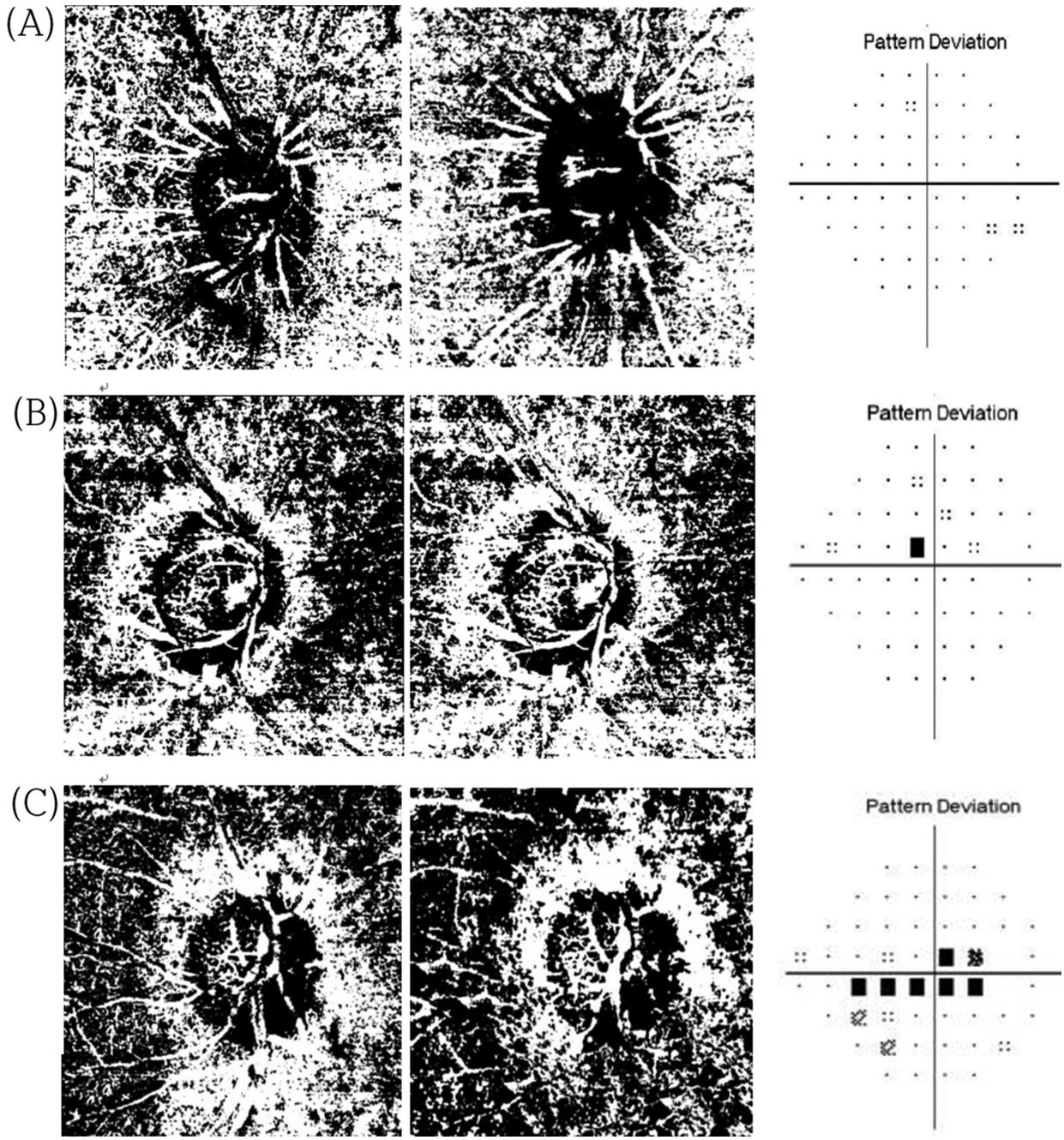

Figure 2. Three representative cases with distinctive features. The first and second images are binarized OCTA image of the deep retinal layers of the peripapillary area. We calculated vessel density fluctuation with these two images. The third images are the pattern deviation plot of the visual field exam of SITA 24-2. (**A**) A 57-year-old woman with low chorioretinal deep vessel density fluctuation shows a normal central visual field; (**B**) a 58-year-old woman with minimal chorioretinal deep vessel density fluctuation shows minimal central visual field defect; (**C**) a 56-year-old woman with moderate chorioretinal deep vessel density fluctuation shows obvious central visual field defect.

glaucoma patients with myopia. Because structural changes due to myopia usually does not progress, decreased blood flow is more likely to affect central vision impairment during the disease course. Additionally, including not only VD but also the amount of change in VD, the VD fluctuation as a surrogate of the status of the blood flow to the ONH will be helpful in predicting central VF damage in patients with myopic glaucoma.

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Author Contributions

Conception and design: Hae-Young Lopilly Park and Chan Kee Park.

Analysis and interpretation: Hae-Young Lopilly Park and Chan Kee Park.

Data collection: Kyung Euy Hong and Da-Young Shin.

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