Systemic Arterial Stiffness Is Associated With Structural Progression in Early Open-Angle Glaucoma

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Purpose. The purpose was to identify association between systemic arterial stiffness predicted by brachial-ankle pulse wave velocity (PWV) and initial location of structural progression in early open-angle glaucoma.

Methods. Patients with early open-angle glaucoma who underwent PWV measurements were subjected to a retrospective review of medical records. A total of 160 eyes of 160 patients were subjected to analyses. Patients were categorized into three PWV groups. Structural progression was determined using event-based analysis of the Guided Progression Analysis software of Cirrus optical coherence tomography.

Results. Thirty-eight patients had a PWV of 1400 cm/s or less on both the left and right sides (low PWV, 39.5% females, 53.9 ± 8.8 years old), and 46 patients showed a PWV of 1800 cm/s or more on either side (high PWV; 54.3% females, 71.3 ± 5.8 years old). The rest of the patients had an intermediate PWV (n = 76, 50.0% females, 59.8 ± 8.6 years old). Among patients who showed progression in 69.3 ± 41.5 months, macular ganglion cell–inner plexiform layer (mGCIPL) loss preceded peripapillary retinal nerve fiber layer (ppRNFL) loss in 86.7% of high PWV group (n = 15, 60.0% females, 70.0 ± 6.0 years old) in comparison with 26.7% of the low PWV group (P = 0.002). The PWV was significantly higher in patients whose structural progression was first observed at mGCIPL (1744.1 ± 347.7 cm/s) than patients whose initial location was ppRNFL (1452.0 ± 201.0 cm/s; P = 0.012). A high PWV was associated with increased likelihood of structural progression at mGCIPL (odds ratio, 7.484; 95% confidence interval, 1.212–49.196; P = 0.030) among patients who showed progression.

Conclusions. PWV is a significant predictor of the location of structural progression in open-angle glaucoma. Vascular insufficiency may be an important aspect in the pathogenesis of glaucoma.

Keywords: glaucoma, optical coherence tomography, pulse wave velocity

There are 2 major theories that have been proposed as the biological basis of open-angle glaucoma (OAG): the mechanical and vascular theories. The mechanical theory dictates that elevated IOP puts mechanical stress on retinal ganglion cells and causes irreversible damage.[1] Accordingly, the IOP has been identified as the single most important risk factor in the development and progression of the disease, and current treatment strategies involve various ways to lower the IOP.[2–4] However, the theory does not adequately explain those patients for whom lowering the IOP fails to slow down the progression of the disease. The vascular theory, which posits that at least some of glaucoma are associated with alterations in ocular blood flow, is likely to be more critical in the pathophysiology of glaucoma for these patients.[5] The concept of systemic vascular dysfunction has been actively explored in OAG, especially in normal-tension glaucoma (NTG).[6,7]

The vascular theory is supported by multiple large population studies that have identified cardiovascular disease as a risk factor for diagnosis of OAG.[8–11] Systemic vascular diseases, such as arteriosclerosis, are believed to alter the microvascular environment of optic disc and retina to cause regional vascular insufficiency.[12] Our previous examinations of optical coherence tomography (OCT) angiography in patients with NTG also supported this theory as macular vessel density was found to be significantly reduced in patients who exhibit abnormal systemic arterial stiffness, in the form of elevated pulse wave velocity (PWV).[13] As a follow-up to this previous study, we sought to identify whether abnormal systemic arterial stiffness is associated with structural damage progression in OAG.

Earlier investigations have shown that in most progression cases, structural progression is detected at only one of two sites, the peripapillary retinal nerve fiber layer (ppRNFL) and macular ganglion cell–inner plexiform layer (mGCIPL).[14] Although the two sites are mutually predictive, Hou et al.[15] argued that neither test can replace the other in detection of disease progression in glaucoma. Spectral domain

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OCT has provided quantitative assessments of peripapillary RNFL thickness and macular GCIPL, and several longitudinal studies have since then compared the characteristics of structural damage in the two sites.[16,17] However, little is known about whether systemic conditions affect the location of structural progression. The purpose of this study was to investigate whether systemic arterial stiffness predicts which of the two sites is more likely to show structural progression first on spectral domain OCT.

Methods

Patient Population

The study protocol was approved by the Institutional Review Board of Severance Hospital at Yonsei University. The study adhered to the tenets of the Declaration of Helsinki. A retrospective review of medical records of patients who visited glaucoma clinic at Severance Hospital between January 2010 and December 2020 was performed. Patients who were 40 years or older at the time of diagnosis with OAG were considered eligible for inclusion. Two glaucoma specialists (J.S.L. and H.W.B.) re-evaluated the diagnosis of OAG and any discrepancy was resolved by a third adjudicator (S.Y.L.). Informed consent was waived owing to the retrospective nature of the study. A total of 160 eyes of 160 patients in early stage of the disease were included. OAG was diagnosed when glaucomatous optic disc changes (such as localized or diffused neuroretinal rim thinning, a difference of cup-to-disc ratio greater than 0.2 between two eyes) were noted on stereo-disc photographs, an RNFL defect was identified on either red-free fundus photographs or Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA), and open angle was confirmed with gonioscopy. Standard automated perimetry (24-2 SITA standard, Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc.) was performed and patients with moderate or advanced glaucoma (i.e. defects with a mean deviation of worse than –6 dB or more than 25% points depressed below the 5% level and/or more than 15% of points depressed below the 1% level on a pattern standard deviation plot, or any point within the central 5° with a sensitivity of less than 15 dB according to Hodapp–Parrish—Anderson criteria) based on reliable visual field (VF) tests were excluded from analysis. A reliable VF results were defined by a fixation loss of less than 33% and a false-positive rate of less than 33%. A VF defect was considered glaucomatous if glaucoma hemifield test results were abnormal or if 3 contiguous VF locations on pattern standard deviation were at a significance level of less than 5% and reproduced in the same location on two successive VF tests. Those meeting any of the following criteria were also excluded: (1) a history of ocular surgery other than uncomplicated cataract surgery, (2) a history of ocular disease that may increase IOP to cause secondary glaucoma, (3) ocular manifestation of systemic disease known to affect optic discs such as diabetic retinopathy or retinal vessel occlusion, (4) eyes with pseudoexfoliation or pigment dispersion, (5) a history of ocular trauma, (6) a failure to undergo two consecutive reliable baseline VF examinations (a reliable VF test was defined as fixation loss of ≤33%, a false-negative rate of ≤3%, and a false-positive rate of ≤15%), and (7) fewer than five high signal strength (>6/10) Cirrus OCT tests. When both eyes of a patient were eligible, the right eye was chosen.

Ophthalmologic Examinations

Patients underwent complete ophthalmologic assessments during their initial visit as per routine protocol of our clinic. A medical history was obtained. Visual acuity, refraction error, central corneal thickness and axial lengths were measured. The IOP was obtained with a Goldmann applanation tonometer (Haag-Streit model BQ-900; Haag-Streit, Inc., Bern, Switzerland). Slit-lamp examinations, gonioscopy, and dilated fundus examinations with a 90-diopter lens were conducted. Patients also underwent color disc stereophotography, red-free fundus photography, standard automated perimetry, and Cirrus OCT. Patients were followed every 6 months, and they underwent visual acuity, IOP measurements, anterior segment assessment with slit-lamp, stereoscopic optic disc photography, VF tests, red-free fundus photography, and Cirrus OCT for each visit.

The baseline IOP was defined as the average of two repeated measurements during separate follow-up visits. The standard deviations of all IOP measurements collected at office during follow-up were considered as IOP fluctuations. Two experienced graders (J.S.L. and S.P.) assessed the optic disc stereographs for the presence of optic disc hemorrhage while being masked to the identify of the patients. Optic disc hemorrhage was defined as a sign of hemorrhage within 1 disc diameter of the optic disc border without any association with optic disc edema, papillitis, diabetic retinopathy or retinal vein occlusion. Any discrepancy between the two graders was resolved by a third adjudicator (S.Y.L.).

Pulse Wave Velocity

The brachial–ankle PWV (baPWV) measurements are described in detail elsewhere.[13] In short, baPWV was obtained with volume plethysmography (VP-1000 plus; Omron HealthCare Co. Ltd., Kyoto, Japan) as indicators of systemic arterial stiffness. Trained technicians placed pressure cuffs on all four arms and ankles of a patient, who had rested for at least 10 minutes in supine position before the test. The BaPWV was calculated by dividing the time taken for a pulse wave to travel from an arm to an ankle on 1 side by the distance the wave travelled. The distance of pulse wave travel was extrapolated from a patient's height. Systolic and diastolic blood pressures, mean arterial pressure, and body mass index (BMI) were also recorded by the device at the same time. The ocular perfusion pressure was calculated as the difference between two-thirds of the mean arterial pressure and the average IOP.

Patients were separated into three different groups based on their PWV measurements according to criteria that reflected calculations of cardiovascular risks using baPWV.[18–20] Patients whose baPWV exceeds 1800 cm/s on either side are believed to be at high risk for cardiovascular events, and such patients were classified as high PWV in our analyses. When the PWV from both right and left sides were less than 1800 cm/s but either side showed a baPWV of greater than or equal to 1400 cm/s, they were categorized into the intermediate PWV group. Patients with baPWV of less than 1400 cm/s on both sides were classified as low PWV for this study.

Determination of Structural Progression

Spectral domain OCT was conducted to obtain the thicknesses of RNFL and GCIPL. An event of structural progression was determined based on the results of event-based analysis of guided progression analysis (Carl Zeiss Meditec, Inc). An experienced operator used the Cirrus Fast-Track eye-tracking technology of software version 6.0 (Cirrus OCT,

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Carl Zeiss Meditec, Inc.) to obtain optic disc 200 × 200 cube and macula 512 × 128 cube scans. The thicknesses of the ppRNFL and mGCIPL were recorded. All OCT scans were evaluated for image quality by a single investigator (J.S.L.) and the scans with a signal strength greater than or equal to 6 without artifacts were selected for analysis. The first two OCT scans obtained at initial visit and at first follow-up visit were set as the baseline. The guided progression analysis algorithm of Cirrus OCT aligned superpixels (4 × 4 pixels) and compared the thicknesses of RNFL and GCIPL of subsequent scans with the baseline. The algorithm encoded a superpixel yellow if the difference between the RNFL thicknesses of subsequent OCT scans and that of baseline exceeded the preset test–retest variability, and marked the change as a possible progression. If the difference persisted in a consecutive follow-up, the superpixel was coded red and marked as a likely progression. Structural progression was considered to have occurred at either ppRNFL or mGCIPL when likely progression was noted on two consecutive examinations.

Patients who showed structural progression were subsequently categorized as macular GCIPL first progression or peripapillary RNFL first progression based on criteria established by a previous study.[17] When an individual showed likely progression on two consecutive OCT tests in the macular GCIPL before any form of progression was noted in peripapillary RNFL, they were classified as macular GCIPL first progression. When likely progression was noted in peripapillary RNFL in two consecutive tests before any change was noted in macular GCIPL, they were classified as peripapillary RNFL first progression. Using these criteria, 62 patients who displayed structural progression were categorized. Twenty-six patients showed ppRNFL thinning only, and 27 patients only showed mGCIPL thinning during follow-up. Nine patients showed changes at both ppRNFL and mGCIPL, but ppRNFL loss preceded mGCIPL loss in four of these patients. The other five patients showed mGCIPL loss before ppRNFL loss.

OCT Angiography

OCT angiography (AngioPlex; Carl Zeiss Meditec, Inc.) was performed and 6 × 6 scans of the peripapillary and macular areas were collected. The angiography algorithm has been described in detail elsewhere.[13] In short, the angiography generated en face microvascular images by producing 350 A-scans per B-scan along the horizontal dimension and repeating the process for 350 B-scans. The internal limiting membrane was set as the inner surface of the superficial retinal layer and the outer border of the inner plexiform layer as the outer surface. The AngioPlex software calculated the vessel density by adding the total length of perfused vasculature per unit area of a 6-mm diameter circle. The vessel density of peripapillary and macular areas were recorded. All examinations were individually assessed by an experienced grader (J.S.L.) and scans with motion artifacts or low signal strength (<7/10) were excluded from analysis. Of 160 eyes, OCT angiography scans were available in 116 eyes, and subgroup analyses were performed.

Statistical Analysis

All statistical analyses were conducted with SPSS version 23 (SPSS Inc., Chicago, IL). The Wilk–Shapiro test was carried out to identify the distribution of data. Normally distributed data were presented as mean ± standard deviation, and categorical data were presented as number (percentage). Comparisons between the low, intermediate and high PWV groups were made using one-way ANOVA, and post hoc analyses were performed using Turkey's significant difference test. Categorical variables were compared using χ^2 test. Analysis of covariance was used to compare vessel density between the low, intermediate, and high PWV groups while adjusting for age. Binary logistic regression analyses were performed to identify associations between PWV and structural damage at macular GCIPL. Multivariate logistic regression analyses were adjusted for average IOP, which, when low, has been reported to be associated with predominantly macular GCIPL loss,[17] and for cardiovascular risk factors (age,[21] sex,[21] BMI,[21] hypertension,[22] and dyslipidemia[21]) as done in previous studies.[23] A P value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Comparisons of baseline characteristics between the three PWV groups are presented in Table 1. Patients were followed for 69.3 ± 41.5 months. The average age advanced as PWV increased (54.0 ± 8.8 years for low, 59.8 ± 8.6 years for intermediate, 71.3 ± 5.8 for high PWV; $P < 0.001$). The proportions of patients diagnosed with hypertension ($P = 0.004$) and diabetes mellitus ($P = 0.003$) also increased as PWV increased. Axial length was shorter in the high PWV group (23.7 ± 0.9 mm) in comparison with both the low and intermediate PWV groups (24.7 ± 1.4 mm for low, 24.5 ± 1.5 mm for intermediate; $P = 0.004$). No significant difference was found in the proportions of females, BMI or follow-up duration. There was no difference in baseline, mean, peak and standard deviations of IOP between the three groups ($P > 0.05$) or the type of antiglaucoma medications. The baseline VFs were comparable between the three groups (mean deviation, –2.3 ± 2.3 dB for low, –2.7 ± 1.9 dB for intermediate, –3.3 ± 2.0dB for high PWV; $P > 0.050$). The final RNFL and GCIPL thicknesses were also comparable for the three groups. No difference was found in the proportions of patients who showed structural progression (either ppRNFL or mGCIPL thinning) during follow-up ($P = 0.577$).

Comparisons of Proportions of mGCIPL Thinning

Structural progression was noted in 62 patients during 69.3 ± 41.5 months of follow-up. These patients who showed structural progression during follow-up from each group were singled out for comparisons (Table 2). The differences in age ($P < 0.001$) maintained trends similar to the entire patient population. However, the differences in the proportions of hypertension and diabetes mellitus and axial lengths were no longer found. The proportions of females, BMI and follow-up duration were not significantly different between the three groups. The IOP at baseline, on average and at peak, were comparable for all three groups. The baseline VF mean deviation and pattern standard deviation as well as final RNFL thickness and GCIPL thickness were found to be comparable as well. When patients who initially showed structural progression at macular GCIPL were counted separately, the proportions were significantly higher in the high PWV group (86.7%) in comparison with the low (26.7%) and intermediate PWV groups (40.6%; $P = 0.002$). Macular GCIPL

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Table 1. Baseline Characteristics of PWV Groups

	Low PWV ($n = 38$)	Intermediate PWV ($n = 76$)	High PWV ($n = 46$)	*P* Value
Age at diagnosis (years)	54.0 ± 8.8	59.8 ± 8.8*	71.3 ± 5.8†‡	<0.001
Female, *n* (%)	15 (39.5)	38 (50.0)	25 (54.3)	0.380
Axial length (mm)	24.7 ± 1.4	24.5 ± 1.5	23.7 ± 0.9†‡	0.004
NTG, *n* (%)	34 (89.5)	71 (93.4)	42 (91.3)	0.757
IOP (mm Hg)				
Baseline	16.4 ± 3.4	16.1 ± 3.5	16.0 ± 3.3	0.838
Mean	13.6 ± 1.9	13.9 ± 1.9	13.6 ± 2.1	0.788
Peak	17.0 ± 3.7	17.7 ± 4.4	17.3 ± 5.0	0.710
Fluctuation	1.9 ± 0.7	1.8 ± 0.8	1.9 ± 0.9	0.977
CCT (µm)	531.8 ± 30.8	538.8 ± 38.0	542.9 ± 27.6	0.640
Visual field (dB)				
Baseline MD	–2.3 ± 2.3	–2.7 ± 1.9	–3.3 ± 2.0	0.070
Baseline PSD	3.7 ± 2.9	3.2 ± 1.9	3.8 ± 2.2	0.528
Final RNFL thickness (µm)	79.5 ± 12.7	74.3 ± 12.5	75.5 ± 9.5	0.085
Final GCIPL thickness (µm)	61.7 ± 13.8	61.7 ± 11.9	58.4 ± 14.8	0.363
Disc hemorrhage, *n* (%)	4 (10.5)	12 (15.8)	13 (28.3)	0.084
Antiglaucoma medications, *n* (%)				
ß-Blockers	15 (39.5)	32 (42.1)	14 (30.4)	0.394
Brimonidine	6 (15.8)	11 (14.5)	9 (19.6)	0.788
CAI	13 (34.2)	27 (35.5)	12 (26.1)	0.510
PG analogues	23 (60.5)	45 (59.2)	26 (56.5)	0.908
PWV (cm/s)				
Right	1249.2 ± 87.3	1558.8 ± 135.3*	2087.8 ± 351.9†‡	<0.001
Left	1244.5 ± 94.5	1572.7 ± 130.1*	2109.7 ± 351.9†‡	<0.001
Underlying conditions, *n* (%)				
HTN	16 (42.1)	39 (51.3)	35 (76.1)	0.004
DM	6 (15.8)	32 (42.1)	23 (50.0)	0.003
Dyslipidemia	9 (23.7)	21 (27.6)	8 (17.4)	0.414
SBP (mm Hg)	118.3 ± 11.2	127.1 ± 10.9*	142.7 ± 18.2†‡	<0.001
DBP (mm Hg)	72.5 ± 8.8	76.6 ± 8.5*	80.5 ± 11.2†‡	0.001
MAP (mm Hg)	88.1 ± 7.9	96.2 ± 11.4*	105.5 ± 16.1†‡	<0.001
BMI (kg/m)	23.7 ± 3.3	24.4 ± 3.0	24.0 ± 3.5	0.588
Progression, *n* (%)	15 (39.5)	32 (42.1)	15 (32.6)	0.103
Follow-up duration (mo)	63.4 ± 41.5	72.5 ± 44.9	70.8 ± 44.6	0.577

$P < 0.05$ was considered statistically significant.

CAI, carbonic anhydrase inhibitors; CCT, central corneal thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; GCIPL ganglion cell–inner plexiform layer; HTN, hypertension; MAP, mean arterial pressure; MD, mean deviation; PG, prostaglandin; PSD, pattern standard deviation; SBP, systolic blood pressure.

*$P < 0.05$ by post hoc analysis when low PWV was compared with intermediate PWV

†$P < 0.05$ by post hoc analysis when low PWV was compared with high PWV

‡$P < 0.05$ by post hoc analysis when intermediate PWV was compared with high PWV.

was the frequent location of the initial structural progression for patients with a high PWV when they showed structural progression.

Comparisons Depending on the Location of the Initial Structural Progression

Patients were recategorized into no progression, ppRNFL first, and mGCIPL first groups depending on the location of initial structural progression (Supplementary Table S1). According to our analyses, patients who showed structural progression first in the form of macular GCIPL thinning tended to be older on average (65.1 ± 8.9 years vs. 57.0 ± 8.5 years ppRNFL first progression; $P = 0.008$). No difference was found in the average, peak, and baseline IOP. The difference in follow-up duration was also not statistically significant ($P = 0.691$). Both systolic and diastolic BP were found to be comparable. However, when the PWV was compared for both the right and left sides, patients who initially showed mGCIPL thinning tended to have higher PWV on both sides (1744.1 ± 347.7 cm/s vs. 1452.0 ± 201.0 cm/s for right; $P = 0.012$ [Fig. A]; 1730.5 ± 346.7 cm/s vs. 1457.0 ± 205.7 cm/s for left; $P = 0.022$ [Fig. B]).

Vessel Density at Macula and Optic Disc of Different PWV Groups

Vessel densities of the superficial RNFLs in macular and peripapillary regions were collected for comparisons between the three PWV groups (Table 3). When comparisons were made irrespective of whether patients showed structural progression, patients with a high PWV showed lower vessel density in the center of macula (6.2 ± 2.9 mm^{-1}) in comparison with the low PWV group (8.3 ± 2.7 mm^{-1}; $P = 0.002$) after controlling for age. The differences in macular vessel density were consistent when patients who showed structural thinning were separately compared. Patients of high PWV who showed structural progression (ppRNFL thinning or mGCIPL thinning) had vessel density of 5.7 ± 2.5 mm^{-1} in the center of macula, which was significantly lower than

Table 2. Comparison of Progressors Between PWV Groups

	Low PWV (n = 15)	Intermediate PWV (n = 32)	High PWV (n = 15)	P Value
Age at diagnosis (years)	57.3 ± 7.0	59.1 ± 9.7	70.0 ± 6.0†‡	<0.001
Female, n (%)	9 (60.0)	16 (50.0)	9 (60.0)	0.732
Axial length (mm)	24.7 ± 1.4	24.1 ± 1.2	23.6 ± 1.0	0.064
NTG, n (%)	13 (86.7)	30 (93.8)	13 (86.7)	0.641
IOP (mm Hg)				
Baseline	17.2 ± 4.1	16.3 ± 4.0	16.3 ± 3.6	0.781
Mean	13.6 ± 2.5	14.0 ± 2.1	13.8 ± 1.6	0.825
Peak	17.2 ± 4.5	18.3 ± 5.9	19.1 ± 7.3	0.693
Fluctuation	2.0 ± 0.8	1.9 ± 1.0	2.2 ± 1.4	0.603
CCT (µm)	531.6 ± 35.1	542.6 ± 41.4	540.5 ± 23.3	0.645
Visual field (dB)				
Baseline MD	−3.4 ± 1.9	−2.8 ± 2.1	−3.5 ± 2.6	0.539
Baseline PSD	5.1 ± 3.6	4.0 ± 1.6	4.5 ± 2.6	0.074
Final RNFL thickness (µm)	75.6 ± 9.4	73.3 ± 13.6	72.0 ± 12.8	0.721
Final GCIPL thickness (µm)	59.1 ± 9.8	58.2 ± 11.5	52.1 ± 15.9	0.228
Rate of change (µm/y)				
ppRNFL	−2.8 ± 3.6	−1.9 ± 2.0	−1.4 ± 2.4	0.417
mGCIPL	−1.1 ± 0.9	−1.4 ± 1.6	−1.6 ± 1.1	0.647
Disc hemorrhage, n (%)	3 (20.0)	6 (18.8)	6 (40.0)	0.259
Antiglaucoma medications, n (%)				
ß-Blockers	6 (40.0)	14 (43.8)	3 (20.0)	0.290
Brimonidine	2 (13.3)	5 (15.6)	3 (20.0)	0.881
CAI	7 (46.7)	13 (40.6)	3 (20.0)	0.279
PG analogues	8 (53.3)	18 (56.3)	9 (60.0)	0.939
PWV (cm/s)				
Right	1271.5 ± 57.5	1544.7 ± 137.2*	2039.1 ± 222.5†‡	<0.001
Left	1261.6 ± 61.6	1544.1 ± 132.2*	2028.6 ± 228.2†‡	<0.001
Underlying conditions, n (%)				
HTN	8 (53.3)	20 (62.5)	10 (66.7)	0.705
DM	2 (13.3)	15 (46.9)	7 (46.7)	0.059
Dyslipidemia	4 (26.7)	9 (28.1)	5 (33.3)	0.920
SBP (mm Hg)	118.1 ± 13.2	126.3 ± 8.6*	140.5 ± 15.3†‡	<0.001
DBP (mm Hg)	71.5 ± 8.6	75.3 ± 8.9	79.1 ± 10.2	0.087
MAP (mm Hg)	87.4 ± 8.7	97.5 ± 14.6*	103.5 ± 14.8†	0.008
BMI (kg/m)	22.9 ± 3.0	24.1 ± 3.0	23.7 ± 4.0	0.524
mGCIPL first progression, n (%)	4 (26.7)	13 (40.6)	13 (86.7)	0.002
Follow-up duration (mo)	55.2 ± 38.9	80.4 ± 45.0	71.3 ± 43.6	0.182

$P < 0.05$ was considered statistically significant.

CAI, carbonic anhydrase inhibitor; CCT, central corneal thickness; DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; MAP, mean arterial pressure; MD, mean deviation; PG, prostaglandin; PSD, pattern standard deviation; SBP, systolic blood pressure.

* $P < 0.05$ by post hoc analysis when low PWV was compared with intermediate PWV

† $P < 0.05$ by post hoc analysis when low PWV was compared with high PWV

‡ $P < 0.05$ by post hoc analysis when intermediate PWV was compared with high PWV.

that of low PWV (8.8 ± 3.2 mm^{-1}; $P = 0.031$) after adjusting for age. Reduced vessel density was also noted in the outer regions of macula as the high PWV group showed a vessel density of 14.2 ± 1.6 mm^{-1} in the region in comparison to 17.0 ± 1.9 mm^{-1} of the low PWV group ($P = 0.031$) after adjusting for age.

Prediction of the Initial Structural Progression Location

Logistic regression analyses were performed to identify any association between the PWV and the location of initial structural progression (Table 4). Of the three PWV types, only a high PWV was significantly associated with initial structural progression at mGCIPL in univariate analyses (odds ratio [OR], 11.471; 95% confidence interval [CI], 2.308–56.996; $P = 0.003$). When the average IOP was adjusted, a high PWV remained statistically significant (OR, 11.810; 95% CI, 2.356–59.197; $P = 0.003$). In a multivariate analysis model in which cardiovascular risk factors, such as age, sex, dyslipidemia, hypertension, and BMI, were adjusted, a high PWV was a significant risk factor for mGCIPL loss preceding ppRNFL loss (OR, 7.283; 95% CI, 1.191–44.552; $P = 0.032$). When both the average IOP and cardiovascular risk factors were adjusted, having a PWV of 1800 cm/s or greater on either side (high PWV) was found to significantly increase the likelihood of mGCIPL being the location of initial structural progression by 7.484 fold (95% CI, 1.212–46.196; $P = 0.030$).

Discussion

In this study, the association between systemic arterial stiffness and the site of initial structural damage in OAG has been investigated. According to our analyses, the proportions of progression are comparable between different PWV

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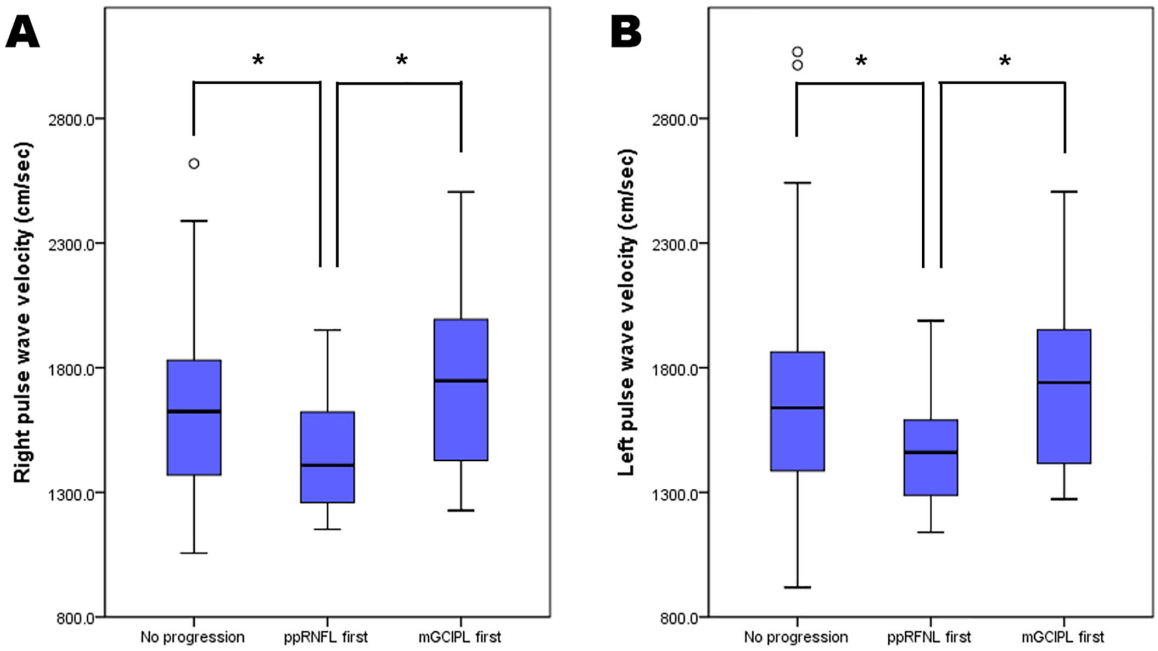

Figure. Comparisons of PWV depending on the location of initial structural progression. Patients who showed structural progression at mGCIPL first showed significantly higher PWV on both right (**A**) and left (**B**) sides in comparison to those who showed initial structural progression at ppRNFL. *$P < 0.05$.

Table 3. A Subgroup Analysis of Vessel Density of 3 PWV Groups at Baseline and Among Progressors

Vessel Density (mm^{-1})	Low PWV ($n = 31$)	Intermediate PWV ($n = 56$)	High PWV ($n = 29$)	*P* Value
All patients				
Disc signal strength[§]	8.8 ± 1.0	8.7 ± 1.0	8.6 ± 1.2	0.668
Disc - full[#]	16.3 ± 1.9	15.2 ± 2.9	15.1 ± 2.7	0.339
Disc - center[#]	1.4 ± 1.8	3.6 ± 1.9	1.9 ± 3.4	0.743
Disc - inner[#]	15.0 ± 2.3	14.2 ± 2.9	14.1 ± 2.9	0.321
Disc - outer[#]	17.5 ± 1.8	16.0 ± 3.1	16.1 ± 2.6	0.145
Macula signal strength[§]	9.0 ± 1.1	8.6 ± 1.1	8.7 ± 1.0	0.353
Macula - full[#]	16.2 ± 2.1	15.3 ± 2.7	14.9 ± 2.8[†]	0.028
Macula - center[#]	8.3 ± 2.7	6.6 ± 3.3[*]	6.2 ± 2.9[†]	0.002
Macula - inner[#]	16.6 ± 3.7	15.7 ± 3.6	15.8 ± 3.0	0.336
Macula - outer[#]	16.3 ± 2.3	15.4 ± 2.6	14.9 ± 2.9	0.107
Vessel Density (mm^{-1})	**Low PWV ($n = 14$)**	**Intermediate PWV ($n = 21$)**	**High PWV ($n = 11$)**	***P* Value**
Progression only				
Disc signal strength[§]	9.4 ± 0.9	8.7 ± 0.9	8.8 ± 1.3	0.188
Disc - full[#]	16.5 ± 2.1	15.1 ± 3.5	14.6 ± 3.1	0.739
Disc - center[#]	1.2 ± 1.2	1.0 ± 1.8	1.8 ± 4.2	0.270
Disc - inner[#]	14.8 ± 2.4	13.7 ± 3.3	13.0 ± 3.7	0.885
Disc - outer[#]	17.6 ± 1.9	16.0 ± 3.8	16.0 ± 3.1	0.566
Macula signal strength[§]	9.3 ± 1.1	8.4 ± 1.0	8.7 ± 1.3	0.134
Macula - full[#]	16.5 ± 2.2	15.2 ± 2.6	15.0 ± 2.0	0.343
Macula - center[#]	8.8 ± 3.2	6.1 ± 2.9[*]	5.7 ± 2.5[†]	0.031
Macula - inner[#]	16.4 ± 5.0	14.9 ± 3.7	16.3 ± 2.1	0.477
Macula - outer[#]	17.0 ± 1.9	15.3 ± 2.6	14.2 ± 1.6[‡]	0.032

$P < 0.05$ was considered statistically significant.
[§] Statistical significance tested by one-way ANOVA
[#] Statistical significance tested by analysis of covariance adjusting for age
[*] $P < 0.05$ by post hoc analysis when low PWV was compared with intermediate PWV.
[†] $P < 0.05$ by post hoc analysis when low PWV was compared with high PWV.
[‡] $P < 0.05$ by post hoc analysis when intermediate PWV was compared with high PWV.

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Table 4. Multivariate Logistic Regression Analysis of iNitial Progression at mGCIPL Among Patients Who Showed Progression

	Model 1		Model 2		Model 3		Model 4	
	B	*P* Value	β	*P* Value	β	*P* Value	β	*P* Value
Low PWV	0.294	0.061	0.300	0.067	0.458	0.323	0.460	0.322
Intermediate PWV	0.523	0.209	0.499	0.183	0.576	0.383	0.566	0.372
High PWV	11.471	0.003	11.810	0.003	6.810	0.045	7.285	0.041

$P < 0.05$ was considered statistically significant.
Model 1: univariate analysis.
Model 2: adjusted for IOP during follow-up (average IOP).
Model 3: adjusted for cardiovascular risk factors (age, sex, BMI, hypertension, diabetes mellitus, dyslipidemia).
Model 4: adjusted for average IOP and cardiovascular risk factors.
CI, confidence interval.

groups. However, among patients with structural progression, initial damage at the macular GCIPL was more prevalent in patients with a high PWV. In comparison with patients who showed initial structural progression at peripapillary RNFL, patients with early damage at the macular GCIPL showed a higher PWV. Vessel density at the macula was on average lower in patients with a high PWV in comparison with those with a low PWV. The difference remained statistically significant when only those patients who showed structural progression were analyzed. Multivariate regression analyses showed that, when progression does occur, a high PWV is associated with initial damage at the macular GCIPL in OAG. To the best of our knowledge, our study is the first to demonstrate the association between systemic arterial stiffness and structural progression of OAG with analyses of longitudinal data.

Systemic arterial stiffness, measured in the form of the PWV, has been recognized as a risk factor for cardiovascular and cerebrovascular diseases for some time.[24–26] Its role in ocular diseases has also been examined, such as branch retinal vein occlusion.[27] No definite conclusions have been drawn on whether increased stiffness of arteries affects the pathogenesis of glaucoma.[28] The Rotterdam Eye Study found a high prevalence of POAG in patients with an increased PWV and low carotid distensibility coefficients, but the results were not statistically significant.[29] In contrast, another study used an ultrasound wall tracking system to illustrate that the distensibility coefficient of the common carotid artery, also indicative of arterial stiffness, is decreased in patients with POAG, concluding that vessel walls are stiffer in patients with POAG than in the controls.[30] The results of some of recent studies have leaned toward a considerable role for arterial stiffness in the pathogenesis of glaucoma as well. One study demonstrated that there exists a correlation between RNFL thickness and regional retinal vessel stiffness in glaucoma; the thinner the RNFL, the more rigid the retinal vessels.[31] Another study noted a correlation between VF defects and systemic arterial stiffness, such that the PWV was lower in patients with NTG with worse VF defects.[12] However, as far as we know, no studies to date have examined the association between systemic vascular conditions and the progression of glaucomatous structural damage over time. In this study, we examined the structural progression of patients with OAG who were followed for 69.3 ± 41.5 months. Our results showed that, among patients with OAG in whom structural damage progressed over time, patients with stiff systemic arteries tended to be affected initially at the macular GCIPL. In other words, macular GCIPL damage in glaucoma is associated with vascular conditions.

Numerous studies show that the site of the initial structural progression holds clinical significance. The initial structural damage site is thought to reflect the mechanism of both initiation and progression of glaucoma. Previously, a study found that macular GCIPL loss tends to appear before peripapillary RNFL loss in glaucoma with low average IOP.[17] The investigators further went on to show that cardiovascular diseases, such as hypertension and myocardial infraction, were predictive of initial structural damage at the macula.[16] Similarly, the majority of the patient population in the present study maintained an IOP of less than 21 mm Hg, and systemic arterial stiffness, reflected in a high PWV, was associated with initial structural damage at macular GCIPL. Among patients who showed progression, those with a high PWV showed significantly higher proportions of early structural progression at macular GCIPL. Our study is an addition to growing evidence that an alternate pathoetiology (other than IOP) exists and that vascular dysfunction plays a major role in the pathogenesis of those subtypes of glaucoma, which exhibits first structural damage in the macular GCIPL.[16] Systemic vascular diseases cause not only microvascular damage at the level of retinal vessels, but also decrease in ocular perfusion pressure.[12] Metabolically active retinal ganglion cells depend on retinal capillary networks for continuous oxygen supply, so retinal hypoperfusion predisposes retinal ganglion cells to injury even when mechanical stress from elevated IOP is absent.[32,33] Further investigations are necessary to identify the mechanisms as well as the means to reverse the pathogenesis.

The lower PWV of the peripapillary RNFL first progression individuals in comparison with those who showed no progression during follow-up were unexpected, because vascular dysfunction has been reported for broad spectrums of OAG in general.[34] One explanation for this result is that individuals with peripapillary RNFL first progression had a lower systemic blood pressure on average in comparison with individuals showing no progression, resulting in a lower PWV.[35] Jammal et al.[36] have recently demonstrated that a lower systemic arterial pressure is associated with faster RNFL loss, after adjustment for IOP. Based on their results, we speculate that individuals who showed predominant peripapillary RNFL loss in our study might have included those who were primarily affected by a low ocular perfusion pressure. Although the difference did not attain statistical significance, the ppRNFL progression group showed relatively lower ocular perfusion pressure in comparison to no progression and mGCIPL progression groups (Supplementary Table S1). Another possible, and perhaps more likely, explanation for the unexpected results is that individuals who showed peripapillary RNFL first progression

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were by chance younger than those who did not show structural progression (Supplementary Table S1), resulting in an increased PWV. The PWV has been shown to increase with age.[37] When age and other cardiovascular risk factors were adjusted, a high PWV continued to show statistically significant associations with macular GCIPL first progression (Table 3). However, the converse was not observed as low PWV was not associated with peripapillary RNFL first progression, after adjustment for the same covariates.

Assessments of macular vessel density in this study have provided us with further evidence that vascular damage plays a critical role in those subtypes of glaucoma in which macular GCIPL loss precedes ppRNFL loss. Various studies have already identified differences in macular vessel density between glaucoma and controls in the past. Rao et al.[38] reported that the parafoveal vessel density was significantly lower in patients with glaucoma than in controls. The mean rates of decrease in macula vessel density, both globally and regionally, were also found to be significantly faster in glaucomatous eyes in comparison with glaucoma suspects and healthy controls.[33] In another study, the rate of macula vessel density decrease was not correlated with IOP.[39] Earlier, our group has shown that macular vessel density is lower in patients with NTG with high PWV in comparison with patients with NTG with a low PWV even after variables such as age were adjusted.[13] In this study, a cross-sectional comparison of patients who showed structural progression revealed that macular vessel density was lower in patients with high PWV. Based on the results from earlier studies as well as those from the current study, we can speculate that, in glaucoma where the IOP is not expected to put overwhelming mechanical stress on retinal ganglion cells, systemic vascular abnormalities may lead to microvascular damage, decreased vessel density, a decrease in the blood supply to ganglion cells in macula, and, in turn, result primarily in mGCIPL loss. However, further investigations are necessary to confirm our speculations, because OCT angiography, the modality adopted for this study, detects vasculature using amplitude correlation from perfused vessels and not the actual flow rate within detected vessels.[33]

Comparisons of IOP-lowering eyedrop use among our patient population did not find any statistically significant difference, but there was a trend toward less frequent use of ß-blockers and carbonic anhydrase inhibitors among patients with a high PWV. Whether this trend is associated with the effect of eyedrops on ocular blood flow is uncertain. Previous studies have shown conflicting evidence on the effect of ß-blockers on ocular blood flow. For instance, Bergstrand et al.[40] noted a significant increase in the resistive index of central retinal artery in patients with POAG on timolol treatment for 1 month, but a prospective study by Lubeck et al.[41] concluded that no notable change was detected in the circulation of optic nerve head after 3 weeks of timolol treatment. Evidence regarding the effect of carbonic anhydrase inhibitors on ocular blood flow is similarly inconclusive. Many studies on dorzolamide found that its use did not modify the parameters associated with blood flow in the ophthalmic artery or central retinal artery.[42,43] As for brinzolamide, a study on rabbits by Barnes et al.[44] showed that blood flow to the optic nerve head increased significantly in comparison to placebo, but the results were not reproduced in patients with glaucoma when Sampaolesi et al.[45] examined them with scanning laser Doppler flowmetry. We speculate that if any IOP-lowering eyedrop does benefit patients with glaucoma by improving ocular blood flow in addition to IOP reduction, the effect is likely to be diminished in patients whose vasculature is abnormally stiff. However, further studies are necessary to identify if arterial stiffness alters the effect of antiglaucoma medication.

Future investigations that study the relations of vascular conditions such as arterial stiffness to other risk factors such as IOP in glaucoma are necessary. The patient population of the present study consisted of those whose baseline IOP was relatively within a normal reference range. How a vascular condition alters the disease progression in the setting of high IOP or large IOP fluctuations is yet unknown. Understanding whether patients with particularly high PWV respond better to certain types of antiglaucoma medications over others may not only help our understanding of the effect of the medication on the disease, but also improve our management of patients with glaucoma. The present study suggests that patients with PWV should be identified early in the course of the disease to guide clinicians to assess their macular region more carefully. We also anticipate that PWV has the potential to single out patients who are less likely to respond to IOP reduction and more likely to benefit from systemic management of vascular conditions.

Although we believe that we have clearly identified an association between systemic arterial stiffness and structural damage at macula, we recognize that the study carries several limitations. First, this study is inherently limited by its retrospective design. Although we were able to find an association between the PWV and initial structural damage at macular GCIPL, we were not able to ascertain a causal relationship owing to the nature of the study design. Second, the number of patients who demonstrated structural damage was small, and the small number may have affected the results. Third, the results of the study may not be generalized; the study population consisted of those referred to a tertiary clinic for specialized management. Fourth, OCT angiography data were available in only some of the patients included, preventing further analyses with angiography data other than cross-sectional comparisons. Last, we did not assess VF progression to determine whether structural damage at the macular GCIPL translated to functional loss in our patients. However, we believe that the relationship between systemic arterial stiffness and preferential site of structural damage in OAG may have been confounded by the subjective nature of a functional measurement of damage such as perimetry.

This study examined the structural progression of patients with OAG with varying degrees of PWV. Longitudinal assessments of structural changes revealed that macular GCIPL loss tended to precede peripapillary RNFL loss in patients with glaucoma with a high PWV. A high PWV was a statistically significant predictor for initial structural damage at the macular GCIPL. The results of this study highlight the importance of cardiovascular disease in the initiation and progression of OAG as well as the need to develop a treatment protocol that does not exclusively involve lowering the IOP.

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Analysis and interpretation: J.S. Lee

Data collection: J.S. Lee, H.W. Bae, S. Park, C.Y. Kim

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