Glaucoma

High Pulse Wave Velocity Is Associated With Decreased Macular Vessel Density in Normal-Tension Glaucoma

Taekjune Lee,1 Hyoung Won Bae,2 Gong Je Seong,2 Chan Yun Kim,2 and Sang Yeop Lee2,3

1Kim Eye Clinic, Cheongju-si, Republic of Korea
2Institute of Vision Research, Department of Ophthalmology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
3Department of Ophthalmology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin-si, Republic of Korea

Correspondence: Sang Yeop Lee, Department of Ophthalmology, Yongin Severance Hospital, Yonsei University College of Medicine, 363, Dongbaekjkukjeon-dae-ro, Giheung-gu, Yongin-si, Gyeonggi-do 16095, Republic of Korea; yeopy@yuhs.ac.

Received: March 5, 2021
Accepted: July 14, 2021
Published: August 16, 2021

Citation: Lee T, Bae HW, Seong GJ, Kim CY, Lee SY. High pulse wave velocity is associated with decreased macular vessel density in normal-tension glaucoma. Invest Ophthalmol Vis Sci. 2021;62(10):12. https://doi.org/10.1167/iovs.21-21995

PURPOSE. To investigate the relationship between pulse wave velocity (PWV) and retinal vessel density (VD) measured by optical coherence tomography angiography (OCTA) in patients with normal-tension glaucoma (NTG).

METHODS. This retrospective study included 103 patients with NTG and 109 healthy controls who underwent glaucoma examination and PWV measurements. Each group was classified into two subgroups according to a brachial-ankle PWV of 1400 cm/s. NTG was diagnosed when the maximum untreated intraocular pressure was < 21 mmHg on three repeated measurements obtained at different times in the presence of glaucomatous optic discs (neuroretinal rim thinning and excavation), peripapillary retinal nerve fiber layer defects, and glaucomatous visual field defects. Healthy controls did not have glaucomatous optic discs or visual field defects and exhibited normal retinal nerve fiber layer thickness. The interval between glaucoma examination and PWV measurements did not exceed six months. Univariate and multivariate logistic regression analyses were performed to identify factors associated with high PWV.

RESULTS. PWV was higher in the NTG group than in the control group, while peripapillary VD and macular VD (mVD) were lower (all P < 0.05). Stepwise logistic regression analysis revealed that high PWV was significantly associated with age, mean arterial pressure (MAP), and mVD in the NTG group. Meanwhile, high PWV was significantly associated with age, MAP, and low-density lipoprotein cholesterol levels in healthy controls.

CONCLUSIONS. High PWV is associated with decreased mVD in NTG patients, suggesting that systemic arterial stiffness might be involved in the pathogenesis of NTG.

Keywords: pulse wave velocity, optical coherence tomography angiography, vessel density, normal-tension glaucoma

Glaucoma is characterized by progressive optic neuropathy with characteristic loss of optic nerve fibers and retinal ganglion cells (RGCs). There are two principal theories for the pathogenesis of glaucoma—a mechanical theory and a vascular theory.2 According to the mechanical theory, intraocular pressure (IOP) causes mechanical stretching of the lamina cribrosa and damage to RGC axons. The vascular theory states that insufficient blood supply due to either increased IOP or other risk factors causes a reduction in ocular blood flow.3–5 The vascular theory is particularly relevant to normal-tension glaucoma (NTG) since glaucomatous optic neuropathy often progresses in spite of low IOP in NTG. Therefore, numerous studies have investigated the relationship between vascular dysregulation and NTG.

Arterial stiffness, which refers to a loss of arterial elasticity, reflects vascular aging. Pulse wave velocity (PWV) is among the methods for representing systemic arterial stiffness and is a useful marker for predicting future cardiovascular events.6–8 PWV has been associated with eye diseases such as diabetic retinopathy,9 retinal vein occlusion,10 and age-related macular degeneration.11 Although several studies have investigated the relationship between PWV and glaucoma, their results have been inconsistent.12–17 Therefore, the role of PWV in glaucoma remains controversial.

The recent introduction of optical coherence tomography angiography (OCTA) allows for the noninvasive measurement of retinal vessel density (VD) in the peripapillary and macular areas.18–20 Studies using OCTA have reported decreased peripapillary and macular VD in glaucomatous eyes compared to healthy eyes.18–22 OCTA has also shown promise for monitoring glaucoma progression.20,23–24 Therefore, OCTA may aid in identifying the pathophysiology of glaucoma as it relates to vascular theory.

Although both measurements may play an important role in determining vascular pathophysiology in NTG, no studies have evaluated the association between PWV and OCTA parameters in NTG. Therefore, the present study aimed to investigate the relationship between PWV and OCTA parameters and to determine which ocular parameters are associated with PWV in patients with NTG.
METHODS

This retrospective cross-sectional study was performed in accordance with the tenets outlined in the Declaration of Helsinki and approved by the Institutional Review Board of Yonsei University (4-2020-0592). The requirement for informed consent was waived due to the retrospective nature of the study. We reviewed the medical records of all patients treated at Severance Hospital from January 2017 to July 2020.

A total of 109 healthy controls and 103 patients with NTG were included in this study. All participants underwent ophthalmologic examinations. All the examinations were carried out as usual for glaucoma patients, or patients who visited our hospital suspected of glaucoma. These included slit-lamp biomicroscopy, Goldmann application tonometry, gonioscopy, dilated fundus examination, measurement of best-corrected visual acuity (BCVA), and measurement of axial length (AXL) (IOL Master; Carl Zeiss Meditec, Dublin, CA, USA). Spectral-domain optical coherence tomography (OCT) (Cirrus HD-OCT, software v11.0; Carl Zeiss Meditec) and standard automated perimetry (Humphrey Field Analyzer II; Carl Zeiss Meditec) were performed to evaluate glaucomatous changes. PWV was usually measured at health check-ups, and blood tests included hemoglobin A1c (HbA1c), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, estimated glomerular filtration rate (eGFR), and uric acid. The interval between glaucoma examination and PWV measurements did not exceed six months.

Inclusion criteria were as follows: (1) age ≥ 40 years; (2) able to confirm open angle on medical records; (3) BCVA ≥ 20/40; and (4) refractive error between ±3 and –6 diopeters (D) spherical and ±3 D cylindrical. NTG was diagnosed when the maximum untreated IOP was < 21 mm Hg on three repeated measurements obtained at different times on separate follow-up visits and in the presence of glaucomatous optic discs (neuroretinal rim thinning and excavation), peripapillary retinal nerve fiber layer (RNFL) defect, and glaucomatous visual field (VF) defects. Glaucomatous VF defects were defined if a cluster of at least three contiguous points had P < 0.05 on the pattern standard deviation plot where at least one of these points had P < 0.01, or if glaucoma hemifield test was outside normal limits. Glaucoma severity stage was based on the Hodapp-Parrish-Anderson criteria. The medical records were re-evaluated by two glaucoma specialists (T.L. and H.W.B.), and images with artifacts or PWV measurements did not exceed six months.

Statistical Analysis

All statistical analyses were performed using the commercially available software SPSS (ver. 23.0; SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as mean and standard deviation. Categorical
variables were summarized as frequencies and percentages. Demographic and clinical data between groups were compared using independent t-tests for continuous parameters and chi-square tests for categorical parameters. Univariate logistic regression analysis was used to identify the factors associated with high PWV in each group. Variables with P values less than 0.2 during the univariate step were further included in a multivariate backward stepwise logistic regression model. In all analyses, P values less than 0.05 were considered to indicate statistical significance.

RESULTS

In total, 109 eyes of 109 healthy controls and 103 eyes of 103 patients with NTG were enrolled. Table 1 presents the baseline characteristics of the study population. Patients in the NTG group were significantly older (P = 0.006) and more frequently had hypertension (P = 0.014) than healthy controls. SBP and MAP were significantly higher (P = 0.011, P = 0.039, respectively), while total cholesterol and LDL cholesterol were lower (P = 0.030, P = 0.004, respectively) in the NTG group than in the control group. PWV was also much faster in the NTG group than in the control group (P = 0.026).

Patients in the NTG group exhibited reduced pVD and mVD when compared to healthy controls (P < 0.001, P = 0.002, respectively). Average RNFL thickness and average ganglion cell–inner plexiform layer (GCIPL) thickness were thinner in the NTG group than in the control group (all P < 0.001). IOP was slightly lower (P = 0.041), and spherical equivalents (SE) were more myopic (P = 0.022) in the NTG group than in the control group, although the difference was relatively small. In the NTG group, the majority of patients (86 eyes, 83.5%) were in the early stage of glaucoma, with a mean deviation better than –6 dB in the VF test. Figure 1 and Figure 2 depict representative cases in the healthy control and NTG groups, respectively.

Table 2 shows demographic characteristics for the low PWV group (PWV < 1400 cm/s) and high PWV group (PWV ≥ 1400 cm/s) in healthy controls. The high PWV group was significantly older (P < 0.001), more hyperopic (P = 0.008), and more frequently had hypertension (HTN) (P < 0.001) than the low PWV group.

A univariate logistic regression analysis revealed that high PWV was significantly associated with age, SBP, DBP, MAP, and SE (all P < 0.05). Variables with P values less than 0.2 were further enrolled in a multivariate model. Since SBP, DBP, and MAP have multicollinearity, MAP was chosen for the multivariate model. A multivariate backward stepwise logistic regression analysis revealed that age (odds ratio (OR) = 1.151, 95% confidence interval (CI) = 1.072–1.237, P < 0.001), MAP (OR = 1.117, 95% CI = 1.060–1.178), and LDL cholesterol (OR = 0.987, 95% CI = 0.974–1.000, P = 0.046) were significantly associated with high PWV in healthy controls (Table 3).

Table 1. Demographic Characteristics in the Healthy Control and NTG Groups

| Systemic parameters | Healthy (n = 109) | NTG (n = 103) | P Value |
|---------------------|------------------|--------------|---------|
| Age (years)         | 58.1 ± 9.1       | 61.6 ± 9.3   | 0.006   |
| Male (%)            | 57 (52.3)        | 55 (53.4)    | 0.872   |
| Body mass index (kg/m²) | 24.0 ± 3.5       | 24.0 ± 3.0   | 0.210   |
| Pulse wave velocity (cm/s) | 1436.6 ± 275.7 | 1537.8 ± 369.0 | 0.025   |
| Hypertension (%)    | 31 (28.4)        | 46 (44.7)    | 0.014   |
| Systolic BP (mmHg)  | 122.2 ± 15.3     | 127.9 ± 17.1 | 0.011   |
| Diastolic BP (mmHg) | 75.1 ± 10.7      | 77.3 ± 10.2  | 0.131   |
| Mean arterial pressure (mmHg) | 90.8 ± 11.8 | 94.2 ± 11.8 | 0.039   |
| Diabetes mellitus (%) | 22 (20.2)        | 22 (21.4)    | 0.833   |
| Hba1C (%)           | 5.9 ± 1.2        | 6.0 ± 1.2    | 0.550   |
| Dyslipidemia (%)    | 33 (30.3)        | 37 (35.9)    | 0.382   |
| Total cholesterol (mg/dL) | 189.2 ± 40.5   | 176.6 ± 43.7 | 0.030   |
| Triglycerides (mg/dL) | 103.4 ± 68.7    | 127.5 ± 84.2 | 0.024   |
| HDL cholesterol (mg/dL) | 53.9 ± 12.8     | 50.6 ± 11.8  | 0.055   |
| LDL cholesterol (mg/dL) | 116.3 ± 38.5    | 101.2 ± 38.1 | 0.004   |
| Chronic kidney disease (%) | 3 (2.8)         | 9 (8.7)     | 0.059   |
| eGFR (ml/min)       | 92.2 ± 14.0      | 86.9 ± 18.5  | 0.019   |
| Uric acid           | 5.3 ± 1.4        | 5.5 ± 1.6    | 0.363   |
| Ocular parameters   |                  |              |         |
| Intraocular pressure (mmHg) | 14.0 ± 2.9      | 13.3 ± 2.0   | 0.041   |
| Axial length (mm)   | 24.2 ± 1.2       | 24.3 ± 1.4   | 0.340   |
| Spherical equivalent (D) | −0.6 ± 1.9     | −1.4 ± 2.8   | 0.022   |
| Average RNFL thickness (μm) | 94.1 ± 8.9     | 77.4 ± 12.3  | <0.001  |
| Average GCIPL thickness (μm) | 82.0 ± 6.0      | 71.8 ± 8.3   | <0.001  |
| Peripapillary VD (mm⁻¹) | 17.2 ± 1.0      | 16.2 ± 1.6   | <0.001  |
| Macular VD (mm⁻¹)   | 16.7 ± 1.7       | 15.9 ± 1.9   | 0.002   |
| Visual field mean deviation (dB) | −3.7 ± 3.6       | −3.7 ± 3.6   |         |
| Glaucoma severity   |                  |              |         |
| Early               | 86 (83.5%)       |              |         |
| Moderate to severe  | 17 (16.5%)       |              |         |

NTG: normal-tension glaucoma; BP: blood pressure; Hba1C: hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; RNFL: retinal nerve fiber layer; GCIPL: ganglion cell–inner plexiform layer; VD: vessel density.
**Table 4** shows demographic characteristics for the low PWV group and high PWV group in patients with NTG. The high PWV group was significantly older \((P < 0.001)\) and more frequently had HTN \((P = 0.002)\), diabetes mellitus (DM) \((P = 0.009)\), and chronic kidney disease \((P = 0.007)\) than the low PWV group. SBP, DBP, MAP (all \(P < 0.001\)), and HbA1c \((P = 0.022)\) were significantly higher, while total cholesterol \((P = 0.030)\) and LDL cholesterol \((P = 0.017)\) were lower in the high PWV group than in the low PWV group. In addition, the high PWV group had significantly shorter AXL \((P = 0.008)\), more hyperopic SE \((P = 0.010)\) and lower pVD \((P = 0.036)\) and mVD \((P < 0.001)\) than the low PWV group.

A univariate logistic regression analysis revealed that high PWV was significantly associated with age, SBP, DBP, MAP, HbA1c, total cholesterol, LDL cholesterol, eGFR, AXL, SE, pVD, and mVD (all \(P < 0.05\)). A multivariate backward stepwise logistic regression analysis revealed that age (OR = 1.228, 95% CI = 1.113–1.356, \(P < 0.001\)), MAP (OR = 1.221, 95% CI = 1.112–1.341, \(P < 0.001\)), and mVD (OR = 0.655, 95% CI = 0.445–0.964, \(P = 0.032\)) were significantly associated with high PWV (Table 5).

**DISCUSSION**

To our knowledge, this is the first study to evaluate the relationship between PWV and retinal VD in NTG. Our findings confirmed that high PWV is associated with decreased mVD in patients with NTG, indicating that systemic arterial stiffness may play a role in the vascular pathophysiology of NTG. The vascular theory is thought to be a main
TABLE 2. Demographic Characteristics of the Low PWV and High PWV Groups in Healthy Controls

|                  | Low PWV (n = 44) (PWV < 1400 cm/s) | High PWV (n = 59) (PWV ≥ 1400 cm/s) | P Value |
|------------------|------------------------------------|--------------------------------------|---------|
| **Systemic parameters** |                                    |                                      |         |
| Age (years)      | 54.6 ± 8.0                         | 62.5 ± 8.4                           | <0.001  |
| Male (%)         | 34                                 | 23                                   | 0.417   |
| Body mass index (kg/m²) | 24.0 ± 3.8                      | 24.0 ± 3.2                           | 0.998   |
| Pulse wave velocity (cm/s) | 1247.6 ± 129.6                | 1676.7 ± 219.1                       | <0.001  |
| Hypertension (%) | 9                                  | 22                                   | <0.001  |
| Systolic BP (mmHg) | 115.9 ± 12.4                     | 130.3 ± 15.1                         | <0.001  |
| Diastolic BP (mmHg) | 71.7 ± 9.4                      | 79.5 ± 10.9                          | <0.001  |
| Mean arterial pressure (mmHg) | 86.4 ± 9.9                     | 96.4 ± 11.8                          | <0.001  |
| Diabetes (%)     | 9                                  | 13                                   | 0.111   |
| HbA1c (%)        | 5.7 ± 1.1                          | 6.1 ± 1.2                            | 0.087   |
| Dyslipidemia (%) | 17                                 | 16                                   | 0.538   |
| Total cholesterol (mg/dL) | 194.6 ± 44.2                   | 182.4 ± 34.7                         | 0.121   |
| Triglycerides (mg/dL) | 97.4 ± 52.5                      | 110.9 ± 84.7                         | 0.312   |
| HDL cholesterol (mg/dL) | 54.4 ± 12.5                    | 53.5 ± 13.2                          | 0.660   |
| LDL cholesterol (mg/dL) | 122.1 ± 39.7                  | 109.1 ± 35.6                         | 0.080   |
| Chronic kidney disease (%) | 2                              | 1                                    | 0.705   |
| eGFR (ml/min)    | 94.0 ± 14.3                        | 90.0 ± 13.4                          | 0.142   |
| Uric acid (mg/dL) | 5.3 ± 1.4                          | 5.4 ± 1.3                            | 0.785   |
| **Ocular parameters** |                                    |                                      |         |
| Intraocular pressure (mmHg) | 13.9 ± 2.9                       | 14.1 ± 3.0                           | 0.771   |
| Axial length (mm) | 24.3 ± 1.2                         | 23.9 ± 1.1                           | 0.065   |
| Spherical equivalent (diopters) | −1.1 ± 1.9                      | −0.1 ± 1.7                           | 0.008   |
| Average RNFL thickness (μm) | 93.9 ± 8.2                        | 94.5 ± 9.7                           | 0.698   |
| Average GCPIPL thickness (μm) | 82.3 ± 5.6                      | 81.6 ± 6.5                           | 0.574   |
| Peripapillary VD (mm⁻¹) | 17.3 ± 1.1                      | 17.1 ± 0.7                           | 0.212   |
| Macular VD (mm⁻¹) | 16.9 ± 1.7                         | 16.5 ± 1.6                           | 0.157   |

PWV: pulse wave velocity; BP: blood pressure; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; RNFL: retinal nerve fiber layer; GCPIPL: ganglion cell–inner plexiform layer; VD: vessel density.

TABLE 3. Univariate and Multivariate Backward Stepwise Logistic Regression Analysis for High PWV (PWV ≥ 1400 cm/s) in the Healthy Control Group

| Variable                      | Univariate Odds Ratio 95% CI P Value | Multivariate Odds Ratio 95% CI P Value |
|-------------------------------|-------------------------------------|---------------------------------------|
| Age, years                    | 1.126 1.064–1.193 <0.001             | 1.151 1.072–1.237 <0.001               |
| Sex, male                     | 1.369 0.641–2.924 0.418              |                                       |
| Body mass index (kg/m²)       | 1.000 0.897–1.114 0.998              |                                       |
| Systolic BP (mmHg)            | 1.083 1.044–1.123 <0.001             |                                       |
| Diastolic BP (mmHg)           | 1.086 1.036–1.137 0.001              |                                       |
| Mean arterial pressure (mmHg) | 1.098 1.048–1.151 <0.001             | 1.117 1.060–1.178 <0.001               |
| HbA1c (%)                     | 1.358 0.936–1.971 0.107              |                                       |
| Total cholesterol (mg/dL)     | 0.992 0.983–1.002 0.123              |                                       |
| Triglycerides (mg/dL)         | 1.003 0.997–1.009 0.317              |                                       |
| HDL cholesterol (mg/dL)       | 0.993 0.964–1.023 0.657              |                                       |
| LDL cholesterol (mg/dL)       | 0.991 0.981–1.001 0.083              | 0.987 0.974–1.000 0.046                |
| eGFR (ml/min)                 | 0.979 0.952–1.007 0.146              |                                       |
| Uric acid (mg/dL)             | 1.040 0.787–1.376 0.782              |                                       |
| Intraocular pressure (mmHg)   | 1.020 0.895–1.161 0.768              |                                       |
| Axial length (mm)             | 0.728 0.517–1.025 0.069              |                                       |
| Spherical equivalent (diopters) | 1.358 1.072–1.721 0.011             |                                       |
| Average RNFL thickness (μm)   | 1.009 0.966–1.053 0.695              |                                       |
| Average GCPIPL thickness (μm) | 0.982 0.921–1.046 0.570              |                                       |
| Peripapillary VD (mm⁻¹)       | 0.782 0.522–1.171 0.252              |                                       |
| Macular VD (mm⁻¹)             | 0.850 0.678–1.065 0.158              |                                       |

Hosmer-Lemeshow P value: 0.068
Nagelkerke R² = 0.492

Variables with P values less than 0.2 during the univariate step were further enrolled in a backward stepwise logistic regression model.

PWV: pulse wave velocity; CI: confidence interval; BP: blood pressure; Hb: hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; RNFL: retinal nerve fiber layer; GCPIPL: ganglion cell–inner plexiform layer; VD: vessel density.
Average GCIPL thickness (μm) 72.7 ± 0.8
Average RNFL thickness (μm) 78.7 ± 0.8
Spherical equivalent (D) 12 ± 0.8
Axial length (mm) 24.8 ± 0.8
Intraocular pressure (mmHg) 12.9 ± 0.8

- **Ocular parameters**
  - Uric acid 5.8 ± 0.8
  - Diabetes (%) 4 ± 0.8
  - Dyslipidemia (%) 14 ± 0.8
  - Total cholesterol (mg/dL) 187.4 ± 37.9
  - Triglycerides (mg/dL) 129.2 ± 91.2
  - HDL cholesterol (mg/dL) 51.9 ± 10.6
  - LDL cholesterol (mg/dL) 111.5 ± 35.4
  - Chronic kidney disease (%) 0 ± 0
  - eGFR (ml/min) 94.7 ± 14.0
  - Urac acid 5.8 ± 1.6

- **Systemic parameters**
  - Age (years) 56.3 ± 7.2
  - Male (%) 28 ± 28
  - Body mass index (kg/m²) 24.3 ± 3.1
  - Pulse wave velocity (cm/s) 1242.0 ± 90.4
  - Hypertension (%) 12 ± 12
  - Systolic BP (mmHg) 116.7 ± 11.6
  - Diastolic BP (mmHg) 72.6 ± 8.3
  - Mean arterial pressure (mmHg) 87.3 ± 9.0
  - Diabetes (%) 4 ± 4
  - HbA1c (%) 5.7 ± 0.8
  - Dyslipidemia (%) 14 ± 14
  - Total cholesterol (mg/dL) 187.4 ± 37.9
  - Triglycerides (mg/dL) 129.2 ± 91.2
  - HDL cholesterol (mg/dL) 51.9 ± 10.6
  - LDL cholesterol (mg/dL) 111.5 ± 35.4
  - Chronic kidney disease (%) 0 ± 0
  - eGFR (ml/min) 94.7 ± 14.0
  - Urac acid 5.8 ± 1.6

**Table 4**. Demographic Characteristics of the Low PWV and High PWV Groups in the NTG Group

| Value | Low PWV (n = 44) | High PWV (n = 59) | P Value |
|-------|----------------|-----------------|---------|
| Age (years) | 56.3 ± 7.2 | 65.6 ± 8.7 | <0.001 |
| Male (%) | 28 | 27 | 0.072 |
| Body mass index (kg/m²) | 24.3 ± 3.1 | 23.6 ± 2.8 | 0.232 |
| Pulse wave velocity (cm/s) | 1242.0 ± 90.4 | 1758.3 ± 342.8 | <0.001 |
| Hypertension (%) | 12 | 34 | 0.002 |
| Systolic BP (mmHg) | 116.7 ± 11.6 | 136.3 ± 15.7 | <0.001 |
| Diastolic BP (mmHg) | 72.6 ± 8.3 | 80.7 ± 10.2 | <0.001 |
| Mean arterial pressure (mmHg) | 87.3 ± 9.0 | 99.3 ± 11.0 | <0.001 |
| Diabetes (%) | 4 | 18 | 0.009 |
| HbA1c (%) | 5.7 ± 0.8 | 6.2 ± 1.4 | 0.022 |
| Dyslipidemia (%) | 14 | 2 | 0.453 |
| Total cholesterol (mg/dL) | 187.4 ± 37.9 | 168.6 ± 46.2 | 0.030 |
| Triglycerides (mg/dL) | 129.2 ± 91.2 | 126.3 ± 79.4 | 0.860 |
| HDL cholesterol (mg/dL) | 51.9 ± 10.6 | 49.7 ± 12.7 | 0.356 |
| LDL cholesterol (mg/dL) | 111.5 ± 35.4 | 93.5 ± 38.5 | 0.017 |
| Chronic kidney disease (%) | 0 | 9 | 0.007 |
| eGFR (ml/min) | 94.7 ± 14.0 | 81.1 ± 19.4 | <0.001 |
| Uric acid | 5.8 ± 1.6 | 5.3 ± 1.5 | 0.121 |

PWV: pulse wave velocity; NTG: normal-tension glaucoma; BP: blood pressure; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; RNFL: retinal nerve fiber layer; GCIPL: ganglion cell–inner plexiform layer; VD: vessel density.

The two most frequently applied measurements of PWV are cfPWV and baPWV. We used baPWV due to its simplicity and noninvasiveness. baPWV is measured simply by wrapping pressure cuffs around the four extremities without taking off clothes and is an independent marker of future cardiovascular events. pulse wave velocity (PWV) is a physical parameter that reflects the arterial stiffness and is used to predict the risk of cardiovascular events. baPWV may be applicable even in those with a low risk of cardiovascular disease (CVD), while cfPWV is thought to be applicable in patients with a high risk of CVD. Therefore, baPWV measurements are included in routine health check-up programs in South Korea. Considering the relationship between these measurements and other ocular disorders such as diabetic retinopathy, retinal vein occlusion, and age-related macular degeneration, the result of our study—which identified a correlation between PWV and mVD measured by OCTA in patients with NTG—suggests the necessity of ophthalmologic examination for patients who have high PWV. Although there is a lack of evidence now, if further research confirms that PWV is not only related with glaucoma but also a risk factor that increases the risk of glaucoma development or progression, PWV will be an important test to evaluate the condition of glaucoma patients.

It is well known that NTG is associated with systemic vascular factors and impaired ocular blood flow. Therefore, a relationship between decreased VD and increased systemic arterial stiffness can be expected in patients with NTG. However, the mechanism underlying the association between high systemic arterial stiffness and decreased mVD in NTG remains unclear. One possible explanation is...
In this study, baPWV was significantly associated with mVD but not with pVD. One possible explanation is that there is an NTG subtype in which glaucomatous changes first occur in the macular GCIPL rather than the peripapillary RNFL. Since the SRL of OCTA is composed of the area from the inner limiting membrane to the inner plexiform layer and our study group mainly consisted of patients with early-stage NTG, mVD may have been affected and impaired earlier. Further studies are required to determine the association between PWV and OCTA at different glaucoma stages and in different subtypes of glaucoma along with the pattern of VF progression.

Our findings also revealed that high PWV is associated with age and MAP in both groups. Age is a strong predictor of PWV, and PWV is well known to be dependent on blood pressure at the time of measurement. Age and BP are also among the important factors to consider when interpreting the relationship between PWV and mVD. Moreover, PWV has been associated with DM, abnormal lipid metabolism, smoking, elevated uric acid levels, high body mass index, and chronic kidney disease. Although we included all the possible systemic factors influencing PWV as covariates, mVD was still significantly associated with PWV in patients with NTG in the multivariate logistic regression analysis.

There are some limitations in this study. First, this was a retrospective cross-sectional study, and the association discovered here may not imply a causal relationship. Cautions are needed when interpreting the results. Further study is needed for the mechanism underlying the relationship between systemic arterial stiffness and retinal vessel damage. Lastly, because of its retrospective study design, we were unable to account for all the factors that affect the measurement of PWV and OCTA. Further studies that consider all possible factors are required.

In conclusion, our study demonstrates that high PWV is associated with decreased mVD in patients with NTG, indicating that systemic arterial stiffness might be involved in the pathogenesis of NTG. These results further indicate that clinical diagnosis and treatment of NTG may require consideration of systemic arterial stiffness, which can be confirmed...
by measuring PWV. In addition, further research regarding the role of systemic arterial stiffness in the pathogenesis of NTG is needed.

Acknowledgments

Supported by a research grant from Yongin Severance Hospital, Yonsei University College of Medicine (9-2020-00089). The funding organization had no role in the design or conduct of this research.

Taekjune Lee wrote the manuscript text. Taekjune Lee and Hyoung Won Bae performed the data review and analysis. Song Je Seo and Chan Yun Kim reviewed the original draft and made revisions. The critical and final revision of the manuscript was performed by Sang Yeop Lee. All authors reviewed the manuscript.

Disclosure: T. Lee, None; H.W. Bae, None; G.J. Seong, None; C.Y. Kim, None; S.Y. Lee, None

References

1. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004;363:1711–1720.
2. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. Surv Ophthalmol. 1994;39:23–42.
3. Cioffi GA, Sullivan P. The effect of chronic ischemia on the primate optic nerve. Eur J Ophthalmol. 1999;9(Suppl 1):S34–S36.
4. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res. 2002;21:359–393.
5. Katai N, Yoshimura N. Apoptotic retinal neuronal death by ischemia-reperfusion is executed by two distinct caspase family proteases. Invest Ophthal Vis Sci. 1999;40:2697–2705.
6. Ohkuma T, Ninomiya T, Tomiyama H, et al. Brachial-ankle pulse wave velocity and the risk prediction of cardiovascular disease: an individual participant data meta-analysis. Hypertension. 2017;69:1045–1052.
7. Tomiyama H, Matsumoto C, Shima K, et al. Brachial-ankle PWV: current status and future directions as a useful marker in the management of cardiovascular disease and/or cardiovascular risk factors. J Atheroscler Thromb. 2016;23:128–146.
8. Ogawa O, Hiraoka K, Watanabe T, et al. Diabetic retinopathy is associated with pulse wave velocity, not with the augmentation index of pulse waveform. Cardiotoxic Diabetol. 2008;7:11.
9. Liu SC, Chuang SM, Shih HM, et al. High pulse wave velocity is associated with the severity of diabetic retinopathy in patients with type 2 diabetes. J Investig Med. 2020;68:1159–1165.
10. Kaderli AA, Kaderli B, Gullulu S, et al. Impaired aortic stiffness and pulse wave velocity in patients with branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol. 2010;248:369–374.
11. Sato E, Feke GT, Appelbaum EY, et al. Association between systemic arterial stiffness and age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2006;244:963–971.
12. Bossuyt J, Vandekerckhove G, De Backer TL, et al. Vascular dysregulation in normal-tension glaucoma is not affected by structure and function of the microcirculation or macrocirculation at rest: a case-control study. Medicine (Baltimore). 2015;94:e425.
13. Bourouki E, Oikonomou E, Moschos M, et al. Pseudoexfoliative glaucoma, endothelial dysfunction, and arterial stiffness: the role of circulating apoptotic endothelial microparticles. J Glaucoma. 2019;28:749–755.
14. Chiba T, Chiba N, Kashiwagi K. Systemic arterial stiffness in glaucoma patients. J Glaucoma. 2008;17:15–18.
15. Hulsman CA, Vingerling JR, Hofman A, et al. Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. Arch Ophthalmol. 2007;125:805–812.
16. Shim SH, Kim CY, Kim JM, et al. The role of systemic arterial stiffness in open-angle glaucoma with diabetes mellitus. Biomed Res Int. 2015;2015:425835.
17. Turkylilmaz K, Oner V, Cicek Y, et al. Systemic arterial stiffness in patients with pseudoexfoliation glaucoma. J Glaucoma. 2014;23:e108–111.
18. Jia Y, Wei E, Wang X, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. Ophthalmology. 2014;121:1322–1332.
19. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Peripapillary and macular vessel density in patients with glaucoma and single-hemifield visual field defect. Ophthalmology. 2017;124:709–719.
20. Liu L, Jia Y, Takusagawa HL, et al. Optical coherence tomography angiography of the peripapillary retina in glaucoma. JAMA Ophthalmol. 2015;133:1045–1052.
21. Bojkian KD, Chen CL, Wen JC, et al. Optic disc perfusion in primary open angle and normal tension glaucoma eyes using optical coherence tomography-based microangiography. PLoS One. 2016;11:e0154691.
22. Triolo G, Rabiolo A, Shemonski ND, et al. Optical coherence tomography angiography of peripapillary and peripapillary vessel perfusion density in healthy subjects, glaucoma suspects, and glaucoma patients. Invest Ophthal Vis Sci. 2017;58:5713–5722.
23. Ghahari E, Bowd C, Zangwill LM, et al. Association of macular and circumpapillary microvasculature with visual field sensitivity in advanced glaucoma. Am J Ophthal. 2019;204:51–61.
24. Park HY, Shin DY, Jeon SJ, et al. Association between parapapillary choroidal vessel density measured with optical coherence tomography angiography and future visual field progression in patients with glaucoma. JAMA Ophthalmol. 2019;137:681–688.
25. Anderson DR. Automated Static Perimetry. St. Louis: The CV Mosby Co.; 1992.
26. Hodapp E PR, Anderson DR. Clinical Decisions in Glaucoma. St. Louis: The CV Mosby Co.; 1993.
27. Yamashina A, Tomiyama H, Arai T, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. Hypertens Res. 2003;26:615–622.
28. Imanishi R, Seto S, Toda G, et al. High brachial-ankle pulse wave velocity is an independent predictor of the presence of coronary artery disease in men. Hypertens Res. 2004;27:71–78.
29. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/ABC/APC/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:2199–2269.
30. Fan N, Wang P, Tang L, et al. Ocular blood flow and normal tension glaucoma. Biomed Res Int. 2015;2015:308505.
31. Mozaffarieh M, Flammer J. New insights in the pathogenesis and treatment of normal tension glaucoma. Curr Opin Pharmacol. 2013;13:45–49.
32. Buckley C, Hadoke PW, Henry E, et al. Systemic vascular endothelial cell dysfunction in normal pressure glaucoma. *Br J Ophthalmol.* 2002;86:227–232.

33. Pache M, Dubler B, Flammer J. Peripheral vasospasm and nocturnal blood pressure dipping-two distinct risk factors for glaucomatous damage? *Eur J Ophthalmol.* 2003;13:260–265.

34. Cursiefen C, Wisse M, Cursiefen S, et al. Migraine and tension headache in high-pressure and normal-pressure glaucoma. *Am J Ophthalmol.* 2000;129:102–104.

35. Drance S, Anderson DR, Schulzer M, et al. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol.* 2001;131:699–708.

36. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol.* 2014;63:636–646.

37. Killer HE, Pircher A. Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis. *Eye (Lond).* 2018;32:924–930.

38. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol (1985).* 2008;105:1652–1660.

39. Holwerda SW, Kardon RH, Hashimoto R, et al. Aortic stiffness is associated with changes in retinal arteriolar flow pulsatility mediated by local vasodilation in healthy young/middle-age adults. *J Appl Physiol (1985).* 2020;129:84–93.

40. Oettli A, Gugleta K, Kochkorov A, et al. Rigidility of retinal vessel in untreated eyes of normal tension primary open-angle glaucoma patients. *Glaucoma.* 2011;20:303–306.

41. Hood DC, Raza AS, de Moraes CG, et al. Glaucomatous damage of the macula. *Prog Retin Eye Res.* 2013;32:1–21.

42. Hwang YH, Jeong YC, Kim HK, et al. Macular ganglion cell analysis for early detection of glaucoma. *Ophthalmology.* 2014;121:1508–1515.

43. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. *Hypertension.* 2009;54:1328–1356.

44. Kim EJ, Park CG, Park JS, et al. Relationship between blood pressure parameters and pulse wave velocity in normotensive and hypertensive subjects: invasive study. *J Hum Hypertens.* 2007;21:141–148.

45. Sakuragi S, Abhayaratna WP. Arterial stiffness: methods of measurement, physiologic determinants and prediction of cardiovascular outcomes. *Int J Cardiol.* 2010;138:112–118.

46. Spronck B, Heusinkveld MH, Vanmolkot FH, et al. Pressure-dependence of arterial stiffness: potential clinical implications. *J Hypertens.* 2015;33:330–338.

47. Rao HL, Pradhan ZS, Weinreb RN, et al. Determinants of peripapillary and macular vessel densities measured by optical coherence tomography angiography in normal eyes. *J Glaucoma.* 2017;26:491–497.

48. Muller VC, Storp JJ, Kerschke L, et al. Diurnal variations in flow density measured using optical coherence tomography angiography and the impact of heart rate, mean arterial pressure and intraocular pressure on flow density in primary open-angle glaucoma patients. *Acta Ophthalmol.* 2019;97:e844–e849.

49. Shoji T, Zangwill LM, Akagi T, et al. Progressive macular vessel density loss in primary open-angle glaucoma: a longitudinal study. *Am J Ophthalmol.* 2017;182:107–117.

50. Prenner SB, Chirinos JA. Arterial stiffness in diabetes mellitus. *Atherosclerosis.* 2015;238:370–379.

51. Li CH, Wu JS, Yang YC, et al. Increased arterial stiffness in subjects with impaired glucose tolerance and newly diagnosed diabetes but not isolated impaired fasting glucose. *J Clin Endocrinol Metab.* 2012;97:E658–E662.

52. Chung TH, Shim JY, Kwon YJ, et al. High triglyceride to high-density lipoprotein cholesterol ratio and arterial stiffness in postmenopausal Korean women. *J Clin Hypertens (Greenwich).* 2019;21:399–404.

53. Fujiwara Y, Chaves P, Takahashi R, et al. Relationships between brachial-ankle pulse wave velocity and conventional atherosclerotic risk factors in community-dwelling people. *Prev Med.* 2004;39:1135–1142.

54. Tomiyama H, Hashimoto H, Tanaka H, et al. Continuous smoking and progression of arterial stiffening: a prospective study. *J Am Coll Cardiol.* 2010;55:1979–1987.

55. Tomiyama H, Shiina K, Vlachopoulos C, et al. Involvement of arterial stiffness and inflammation in hyperuricemia-related development of hypertension. *Hypertension.* 2018;72:739–745.

56. Tang B, Luo F, Zhao J, et al. Relationship between body mass index and arterial stiffness in a health assessment Chinese population. *Clin J Am Soc Nephrol.* 2020;15:1879–1885.

57. Lioufas NM, Pedagogos E, Hawley CM, et al. Aortic calcification and arterial stiffness burden in a chronic kidney disease cohort with high cardiovascular risk: baseline characteristics of the impact of phosphate reduction on vascular end-points in chronic kidney disease trial. *Am J Nephrol.* 2020;51:201–215.

58. Yoshida M, Tomiyama H, Yamada J, et al. Relationships among renal function loss within the normal to mildly impaired range, arterial stiffness, inflammation, and oxidative stress. *Clin J Am Soc Nephrol.* 2007;2:1118–1124.