

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

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**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).<sup>1</sup> There are two principal theories for the pathogenesis of glaucoma—a mechanical theory and a vascular theory.<sup>2</sup> 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.<sup>3–5</sup> 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.<sup>6,7</sup> PWV has been associated with eye diseases such as diabetic retinopathy,<sup>8,9</sup> retinal vein occlusion,<sup>10</sup> and

age-related macular degeneration.<sup>11</sup> Although several studies have investigated the relationship between PWV and glaucoma, their results have been inconsistent.<sup>12–17</sup> 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.<sup>18,19</sup> Studies using OCTA have reported decreased peripapillary and macular VD in glaucomatous eyes compared to healthy eyes.<sup>19–22</sup> OCTA has also shown promise for monitoring glaucoma progression.<sup>20,23,24</sup> 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 applanation 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  $\geq 40$  years; (2) able to confirm open angle on medical records; (3) BCVA  $\geq 20/40$ ; and (4) refractive error between +3 and -6 diopters (D) spherical and  $\pm 3$  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.<sup>25</sup> Glaucoma severity stage was based on the Hodapp-Parrish-Anderson criteria.<sup>26</sup> The medical records were re-evaluated by two glaucoma specialists (T.L. and H.Y.B.). If the two specialists could not agree on a diagnosis of NTG, the final decision was made by a third glaucoma specialist (S.Y.L.). Healthy controls did not have glaucomatous optic discs or VF defects and exhibited normal RNFL thickness, which was within 95% of the internally set database for OCT results.

Patients with poor data quality or other ocular comorbidities were excluded: (1) signal strength less than 7, images with artifacts; (2) eyes with a diagnosis of pigment dispersion glaucoma, pseudoexfoliative glaucoma, or primary angle-closure glaucoma; (3) retinal disorder (diabetic retinopathy, age-related macular degeneration, retinal detachment, etc.); (4) history of ocular trauma or intraocular surgery; (5) history of brain disorder (brain hemorrhage, brain infarction, brain aneurysm, brain tumor, etc.); and (6) history of optic nerve disorder (optic neuritis, ischemic optic neuropathy, optic coloboma, etc.).

For patients with NTG, the eye with a more severe glaucoma status was chosen as the study eye. If patients had a similar glaucoma severity in both eyes, the study eye was

randomly selected. For patients with healthy eyes, the study eye was also randomly selected.

## Pulse Wave Velocity

Brachial-ankle PWV (baPWV) was measured using volume-plethysmography (VP-1000 plus; Omron HealthCare Co. Ltd., Kyoto, Japan). Trained technicians and physicians placed the pressure cuffs on both arms and both ankles of the patient and performed the measurement after the patient had rested for approximately 10 minutes in the supine position. The travel path from body height was extrapolated, and baPWV was computed automatically by dividing the time difference between the pulse waves that were transmitted to the brachial and ankle arteries by the travel path. The faster value of the right- and left-side baPWV was used for analysis. The device also measured blood pressure (BP) at the same time. Systolic BP (SBP) and diastolic BP (DBP) were measured, and mean arterial pressure (MAP) was calculated as follows:  $[SBP + (2 \times DBP)]/3$ .

We set a baPWV of 1400 cm/s as the reference value since this is what has been identified as an independent risk factor in the Framingham score and can distinguish patients with atherosclerotic cardiovascular disease.<sup>27,28</sup> It is also adopted as a reference value in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.<sup>29</sup>

## OCTA

Under pupil dilation, OCTA (AngioPlex; Carl Zeiss Meditec) images of the peripapillary and macular areas were obtained using a  $6 \times 6$  mm scan. The optical microangiography algorithm analyzed the changes in the complex signal (both intensity and phase changes contained within sequential B-scans performed at the same position) and then generated en face microvascular images. In the  $6 \times 6$  mm scan, there were 350 A-scans in each B-scan along the horizontal dimension, and 350 B-scans were repeated twice at each location. The boundaries of the superficial and deep retinal layers were determined automatically. The inner surface of the superficial retinal layer (SRL) was defined by the internal limiting membrane. The outer surface of the SRL was denoted by the outer border of inner plexiform layer. The segmentation software automatically detected the boundaries of the retinal layers from the structural OCT cross-sectional images by measuring the gradient of OCT signals to create SRL en face images. With the aid of innate software for AngioPlex OCTA, VD was defined as the total length of perfused vasculature per unit area in a region of measurement. The innate software automatically calculated the VD in the center circle with a diameter of 6 mm. It included all the vessels in the area, including large vessels. Thus, peripapillary VD (pVD) and macular VD (mVD) were calculated. All examinations were individually reviewed by two glaucoma specialists (T.L. and H.W.B.), and images with artifacts or signal strength less than 7 were excluded.

## 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  $\geq 1400$  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.

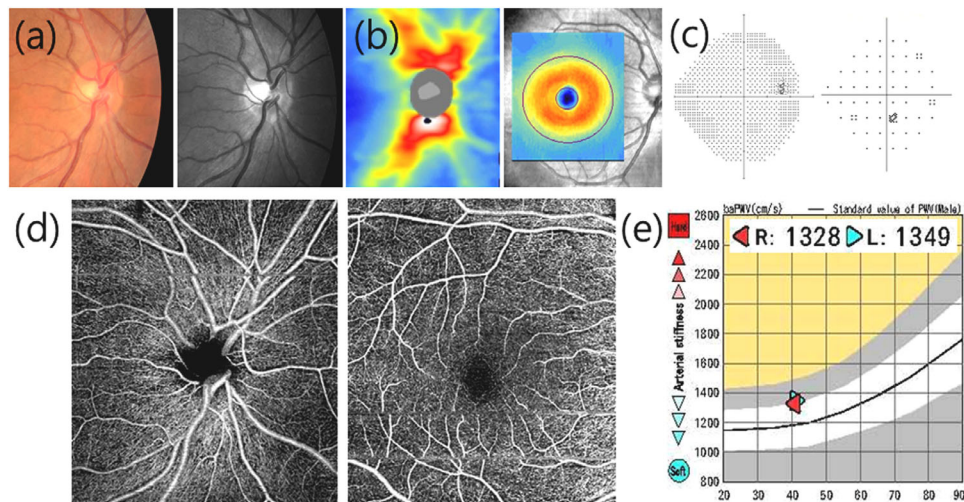
A univariate logistic regression analysis revealed that high PWV was significantly associated with age, SBP, DBP, MAP, and SE (all  $P < 0.05$ ). Variables with *P* values less than 0.2 were further enrolled in a multivariate model. Since SBP, DBP, and MAP have multicollinearity, MAP was chosen for the 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

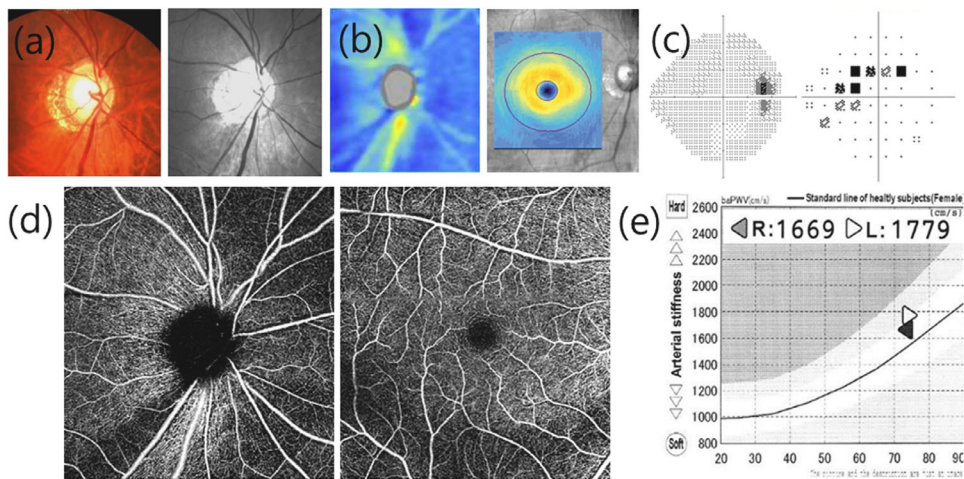
	Healthy ( <i>n</i> = 109)	NTG ( <i>n</i> = 103)	<i>P</i> Value
Systemic parameters			
Age (years)	58.1 ± 9.1	61.6 ± 9.3	0.006
Male (%)	57 (52.3)	55 (53.4)	0.872
Body mass index (kg/m <sup>2</sup> )	24.0 ± 3.5	24.0 ± 3.0	0.210
Pulse wave velocity (cm/s)	1436.6 ± 275.7	1537.8 ± 369.0	0.025
Hypertension (%)	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 ± 38.3	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 <sup>-1</sup> )	17.2 ± 1.0	16.2 ± 1.6	<0.001
Macular VD (mm <sup>-1</sup> )	16.7 ± 1.7	15.9 ± 1.9	0.002
Visual field mean deviation (dB)		-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.





**FIGURE 1.** A representative case in the healthy control group. All examination results were normal. (a) Color and red-free fundus photography; (b) RNFL and GCIPL thickness on OCT; (c) VF; (d) Peripapillary VD and macular VD on OCTA; (e) baPWV. RNFL: retinal nerve fiber layer; GCIPL: ganglion cell-inner plexiform layer; OCT: optical coherence tomography; VF: visual field; VD: vessel density; OCTA: optical coherence tomography angiography; baPWV: brachial-ankle pulse wave velocity.



**FIGURE 2.** A representative case in the NTG group. (a) Color and red-free fundus photography; (b) OCT showed RNFL and GCIPL defects in the inferior region; (c) Paracentral VF defect in the superior hemifield; (d) Peripapillary and macular VD were reduced on OCTA; (e) baPWV was increased to 1669 cm/s (*right*) and 1779 cm/s (*left*). RNFL: retinal nerve fiber layer; GCIPL: ganglion cell-inner plexiform layer; OCT: optical coherence tomography; VF: visual field; VD: vessel density; OCTA: optical coherence tomography angiography; baPWV: brachial-ankle pulse wave velocity.

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/m <sup>2</sup> )	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	53.3 ± 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 GCIPL thickness (μm)	82.3 ± 5.6	81.6 ± 6.5	0.574
Peripapillary VD (mm <sup>-1</sup> )	17.3 ± 1.1	17.1 ± 0.7	0.212
Macular VD (mm <sup>-1</sup> )	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; GCIPL: 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

	Univariate			Multivariate		
	Odds Ratio	95% CI	P Value	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/m <sup>2</sup> )	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 GCIPL thickness (μm)	0.982	0.921–1.046	0.570			
Peripapillary VD (mm <sup>-1</sup> )	0.782	0.522–1.171	0.232			
Macular VD (mm <sup>-1</sup> )	0.850	0.678–1.065	0.158			
Hosmer-Lemeshow P value: 0.068						
Nagelkerke R <sup>2</sup> = 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; GCIPL: ganglion cell–inner plexiform layer; VD: vessel density.

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

	Low PWV (n = 44) (PWV < 1400 cm/s)	High PWV (n = 59) (PWV ≥ 1400 cm/s)	P Value
<b>Systemic parameters</b>			
Age (years)	56.3 ± 7.2	65.6 ± 8.7	<0.001
Male (%)	28	27	0.072
Body mass index (kg/m <sup>2</sup> )	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
<b>Ocular parameters</b>			
Intraocular pressure (mmHg)	12.9 ± 2.0	13.6 ± 1.9	0.057
Axial length (mm)	24.8 ± 1.5	24.0 ± 1.3	0.008
Spherical equivalent (D)	-2.2 ± 3.0	-0.8 ± 2.5	0.010
Average RNFL thickness (μm)	78.7 ± 12.2	76.4 ± 12.4	0.359
Average GCIPL thickness (μm)	72.7 ± 8.1	71.1 ± 8.4	0.343
Peripapillary VD (mm <sup>-1</sup> )	16.6 ± 1.6	15.9 ± 1.5	0.036
Macular VD (mm <sup>-1</sup> )	16.8 ± 1.7	15.3 ± 1.8	<0.001
Visual field mean deviation (dB)	-4.0 ± 4.7	-3.4 ± 2.4	0.436

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.

factor influencing NTG,<sup>30,31</sup> given its relevance to systemic vascular dysregulation, including vascular and endothelial diseases,<sup>32</sup> vasospasm syndrome,<sup>33</sup> and migraine.<sup>34,35</sup> PWV reflects systemic arterial stiffness, and OCTA evaluates the microvascular status of the eye, which is an end organ. The relevance of these two parameters supports the vascular theory of NTG and suggests the importance of systemic vessel status evaluations in patients with NTG.

Although several studies have investigated the relationship between PWV and glaucoma, they have yielded conflicting results. The Rotterdam Eye Study<sup>15</sup> first showed that participants with an increased carotid-femoral PWV (cfPWV) and especially those with a low carotid distensibility coefficient, both indicative of high arterial stiffness, had a higher prevalence of primary open-angle glaucoma (POAG), although the results were not statistically significant. In other studies regarding the relationship between cfPWV and glaucoma, cfPWV exhibited a stepwise increase from healthy controls to patients with POAG and those with pseudoexfoliative glaucoma,<sup>13</sup> and such increases in cfPWV were associated with pseudoexfoliative glaucoma.<sup>17</sup> Other studies evaluated the relationship between baPWV and glaucoma. One study reported that baPWV was positively associated with glaucoma and NTG in particular, while other studies failed to identify a significant difference in baPWV between patients with NTG and healthy controls.<sup>12,14</sup> These diverse results may be due to the different glaucoma subgroups and different modalities used to measure PWV.

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.<sup>6,7</sup> baPWV may be applicable even in those with a low risk of cardiovascular disease (CVD),<sup>6</sup> while cfPWV is thought to be applicable in patients with a high risk of CVD.<sup>36</sup> 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,<sup>8,9</sup> retinal vein occlusion,<sup>10</sup> and age-related macular degeneration,<sup>11</sup> 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.<sup>37</sup> 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



TABLE 5. Univariate and Multivariate Backward Stepwise Logistic Regression Analysis for High PWV (PWV  $\geq$  1400 cm/s) in NTG Group

	Univariate			Multivariate		
	Odds Ratio	95% CI	P Value	Odds Ratio	95% CI	P Value
Age, years	1.153	1.083–1.229	<0.001	1.228	1.113–1.356	<0.001
Sex, male	2.074	0.932–4.615	0.074			
Body mass index (kg/m <sup>2</sup> )	0.921	0.805–1.054	0.233			
Systolic BP (mmHg)	1.123	1.070–1.178	<0.001			
Diastolic BP (mmHg)	1.099	1.045–1.155	<0.001			
Mean arterial pressure (mmHg)	1.131	1.071–1.194	<0.001	1.221	1.112–1.341	<0.001
HbA1c (%)	1.611	1.003–2.589	0.049			
Total cholesterol (mg/dL)	0.990	0.980–0.999	0.034			
Triglycerides (mg/dL)	1.000	0.995–1.004	0.859			
HDL cholesterol (mg/dL)	0.984	0.952–1.018	0.353			
LDL cholesterol (mg/dL)	0.987	0.976–0.998	0.020			
eGFR (ml/min)	0.948	0.919–0.978	0.001			
Uric acid (mg/dL)	0.815	0.628–1.058	0.124			
Intraocular pressure (mmHg)	1.220	0.991–1.503	0.061			
Axial length (mm)	0.675	0.498–0.915	0.011			
Spherical equivalent (diopters)	1.214	1.041–1.417	0.014			
Average RNFL thickness ( $\mu$ m)	0.985	0.954–1.017	0.356			
Average GCIPL thickness ( $\mu$ m)	0.977	0.931–1.025	0.341			
Peripapillary VD (mm <sup>-1</sup> )	0.750	0.570–0.988	0.041			
Macular VD (mm <sup>-1</sup> )	0.605	0.461–0.796	<0.001	0.655	0.445–0.964	0.032
Hosmer-Lemeshow P value:	0.595					
Nagelkerke R <sup>2</sup> =	0.672					

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; 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.

that, although baPWV reflects the stiffness of medium- to large-sized arteries, excessive pressure pulsatility may affect microvascular remodeling and impair the regulation of local blood flow, which can lead to diffuse microscopic tissue damage.<sup>38</sup> This notion is supported by another study, which demonstrated that increased aortic stiffness is inversely correlated with retinal arterial lumen diameter and increased microvascular resistance.<sup>39</sup> Moreover, one study reported that untreated NTG eyes had stiffer retinal vessels and that vessel rigidity correlates with the level of glaucomatous damage.<sup>40</sup> Further studies are required to identify the mechanism underlying the relationship between systemic arterial stiffness and retinal vessel damage.

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.<sup>41,42</sup> 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,<sup>43</sup> and PWV is well known to be dependent on blood pressure at the time of measurement.<sup>44–46</sup> Age and BP are also among the important factors to consider when evaluating retinal VD.<sup>47–49</sup> Therefore, age and BP should be considered when interpreting the relationship between PWV and mVD. Moreover, PWV has been associated with

DM,<sup>50,51</sup> abnormal lipid metabolism,<sup>52,53</sup> smoking,<sup>54</sup> elevated uric acid levels,<sup>55</sup> high body mass index,<sup>56</sup> and chronic kidney disease.<sup>57,58</sup> 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 PWV and mVD in NTG. Second, we only included data with good image quality, as signal strength is an important factor when analyzing OCTA images. Thus, it is possible that selection bias occurred. However, these conditions would have contributed to increasing the reliability of our study results. Third, the sample in this study comprised mostly patients with early-stage NTG (86 eyes, 83.5%). This must be considered when using the results of our study to inform clinical practice, as the relationship may differ in patients with more advanced NTG or other types of glaucoma, such as POAG. Studies comparing POAG with NTG may aid in clarifying the significance of PWV in glaucoma. 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.

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