Changes in Ganglion Cell–Inner Plexiform Layer Thickness and Retinal Microvasculature in Hypertension: An Optical Coherence Tomography Angiography Study

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• PURPOSE: To investigate retinal blood flow in patients with hypertension using optical coherence tomography angiography (OCTA) and the relationship between blood flow metrics and ganglion cell–inner plexiform layer (GC-IPL) thickness.

• DESIGN: Retrospective, cross-sectional study.

• METHODS: A total of 201 eyes from 117 healthy subjects and 84 hypertensive patients without any ocular abnormalities were included. Hypertensive patients were divided into the 2 groups according to disease periods (< 5 years: Hypertension Group 1; ≥5 years: Hypertension Group 2). Macular 3 × 3-mm angiography was acquired using the Zeiss Cirrus 5000 OCT instrument. Vessel density (VD), perfusion density (PD), and foveal avascular zone metrics of the superficial capillary plexus were automatically calculated, and the thicknesses of the central fovea, GC-IPL, and peripapillary retinal nerve fiber layer (RNFL) were measured. All measurements were compared among the 3 groups, and retinal blood flow metrics were correlated with the thickness of each retinal layer. Logistic regression analyses were performed to determine the factors associated with prolonged hypertension.

• RESULTS: The average GC-IPL ($P < .001$) and peripapillary RNFL ($P = .048$) thicknesses in Hypertension Group 2 were significantly thinner compared to the control group. The 3 mm total area of the VD and PD was also decreased compared to the control group and Hypertension Group 1 (all $P < .05$), and was significantly correlated with the GC-IPL (VD: $r = 0.450$, $P = .001$; PD: $r = 0.467$, $P < .001$) and peripapillary RNFL (VD: $r = 0.314$, $P = .027$; PD: $r = 0.328$, $P = .023$) thicknesses in Hypertension Group 2. Using multivariate logistic analyses, only the average GC-IPL thickness was a significant factor for prolonged hypertension (odds ratio = 0.911, $P = .002$).

• CONCLUSIONS: In patients with hypertension lasting more than 5 years, inner retinal layer thinning, particularly GC-IPL thinning, was observed, which was significantly correlated with a decrease in retinal blood flow. Therefore, physicians should consider the effects of hypertension on the GC-IPL. (Am J Ophthalmol 2019;199:167–176. © 2018 Elsevier Inc. All rights reserved.)

HYPERTENSION, A LEADING RISK FACTOR FOR CARdiovascular and cerebrovascular disease, is a major global health problem. Worldwide, approximately 40% of adults aged ≥25 years have been diagnosed with hypertension, and the numbers increased from 600 million in 1980 to 1 billion in 2008.[1] The prevalence increased from 26.4% in 2000 to 31.1% in 2010,[2] although roughly half of the United States population has their blood pressure (BP) under control.[3] Hypertension can cause target end-organ damage, such as cardiovascular disease, stroke, left ventricular failure, and nepropathy, which cause 9.4 million deaths worldwide every year.[4–6] It is also a risk factor for various eye diseases, including retinal vascular occlusion, retinal artery macroaneurysm, and nonarteritic anterior ischemic optic neuropathy, and chronic sustained hypertension can cause hypertensive retinopathy, characterized by retinal hemorrhage, hard exudates, cotton-wool spots, optic disc edema, and macular edema.[7,8]

Several studies have reported that changes in systemic BP can affect ocular blood flow, which is associated with the progression of glaucoma.[9–11] We previously reported that hypertensive patients with no retinal abnormalities or glaucomatous changes showed inner retinal layer thinning including the ganglion cell–inner plexiform layer (GC-IPL) and peripapillary retinal nerve fiber layer (RNFL). We speculated that chronic ischemia caused by retinal microvascular disorders might cause changes in retinal structure,[12] but the mechanism of GC-IPL loss in hypertension has not been clearly elucidated.

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Nov 21, 2018.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.11.016

Optical coherence tomography angiography (OCTA) allows the rapid and noninvasive assessment of the retinal capillary network,[13] facilitating the easy and automatic evaluation of retinal blood flow using various retinal vascular metrics such as vessel density (VD), perfusion density (PD), and foveal avascular zone (FAZ) using built-in OCTA software. In this study, we analyzed retinal microcirculation in hypertensive patients using OCTA, as well as the association between the inner retinal changes and retinal blood flow.

METHODS

• **SUBJECTS:** This was an observational, cross-sectional study. Patients were retrospectively evaluated using medical data recorded at the retina clinic of Chungnam National University Hospital, and the enrolled patients were not included in other studies. The study protocol was approved by the Institutional Review Board of Chungnam National University Hospital (Daejeon, Republic of Korea) and adhered to the tenets of the Declaration of Helsinki.

Patients with diabetes mellitus were excluded because the inner retinal layer could be affected by diabetes. All patients were initially diagnosed with hypertension at the department of internal medicine of Chungnam National University Hospital. The diagnosis of hypertension was made according to the Korean hypertension treatment guideline.[14] The BPs of all patients with hypertension were well under control. BP was stable and antihypertensive medication in all patients had not changed for more than 6 months. Hypertensive patients were classified into 2 groups, according to the duration of hypertension: patients with hypertension <5 years (Hypertension Group 1, 32 eyes) and patients with hypertension ≥5 years (Hypertension Group 2, 52 eyes).

All medical records and fundus photographs were reviewed by 2 independent investigators (H.B.L. and M.W.L.) to determine the hypertensive retinopathy status, and patients with abnormal fundus findings associated with hypertensive retinopathy such as arteriovenous nicking, retinal hemorrhage, cotton-wool spots, and optic disc edema were excluded. All patients had a complete ophthalmic examination including measurement of the best-corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure, dilated fundus examination, photography, axial length using the IOL Master (Carl Zeiss Meditec, Jena, Germany), optical coherence tomography (OCT), and OCTA using the AngioPlex from the Zeiss Cirrus 5000 (Carl Zeiss Meditec, Dublin, California, USA). Fundus images were obtained in 5 areas (center, superior, temporal, inferior, and nasal) with 45-degree field of view using the TRC-NW8 fundus camera (Topcon Medical Systems, Tokyo, Japan). In addition, the BP of all patients was measured with ophthalmic examination by automated BP device in the retinal clinic. If the BP exceeded the normal range, it was measured again and the mean value was recorded.

The exclusion criteria included patients with a history of systemic disease other than hypertension, history of intraocular surgery, glaucoma and glaucoma suspect (enlarged cup-to-disc ratio, asymmetric cup-to-disc ratio, notching or narrowing of the neuroretinal rim, disc hemorrhage, or suspicious alteration in the nerve fiber layer), optic nerve disorders, intraocular pressure >21 mm Hg, spherical equivalent >+3.0 diopters (D) or <-3.0 D, optic disc abnormalities, axial length ≥26.0 mm, or any other optic nerve or retinal dysfunction. If both eyes met the inclusion criteria, 1 eye was randomly selected.

Among the subjects who visited our clinic for various reasons (health screening examination, evaluation for ocular disease, etc), those who met exclusion criteria and had BP records were recruited into the normal control group. The normal control groups also had no history of diabetes or hypertension, had not undergone any prior intraocular surgeries, had normal anterior segment and fundus, and had BCVA ≥20/25 (Snellen), a normal intraocular pressure range, and spherical equivalent within ± 3.0 D.

• **OPTICAL COHERENCE TOMOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY:** All eyes underwent macular angiography imaging with a 3 × 3-mm scan using the Zeiss Cirrus 5000 system (Carl Zeiss Meditec, Dublin, California, USA) under pupil dilation to acquire microvasculature images of the macular areas. This instrument operated at a central wavelength of 840 nm and a speed of 68 000 A-scans per second, and there were 245 A-scans in each B-scan along the horizontal and vertical dimensions in the 3 × 3 scan pattern.[15] The optical microangiography-complex algorithm analyzed the changes in complex signals (both intensity and phase changes contained within the sequential B-scans performed at the same position)[16,17] and then produced en face microvascular images. The vascular images of the superficial capillary plexus (SCP), which spanned from the internal limiting membrane to the inner plexiform layer, and deep capillary plexus, which extended from the inner nuclear layer to the outer plexiform layer, were displayed automatically.

All scans were analyzed using Cirrus OCTA software (AngioPlex, version 10.0). The measurement area of the 3 × 3-mm scan was divided into 5 subfields composed of a 1-mm center and 4 quadrant sectors (superior, inferior, nasal, and temporal) that were identical to the inner circles of the Early Treatment Diabetic Retinopathy Study subfields. VD (defined as the total length of perfused vasculature per unit area in a region of measurement; Figure 1, Top left and Bottom left) and PD (defined as the total area of perfused vasculature per

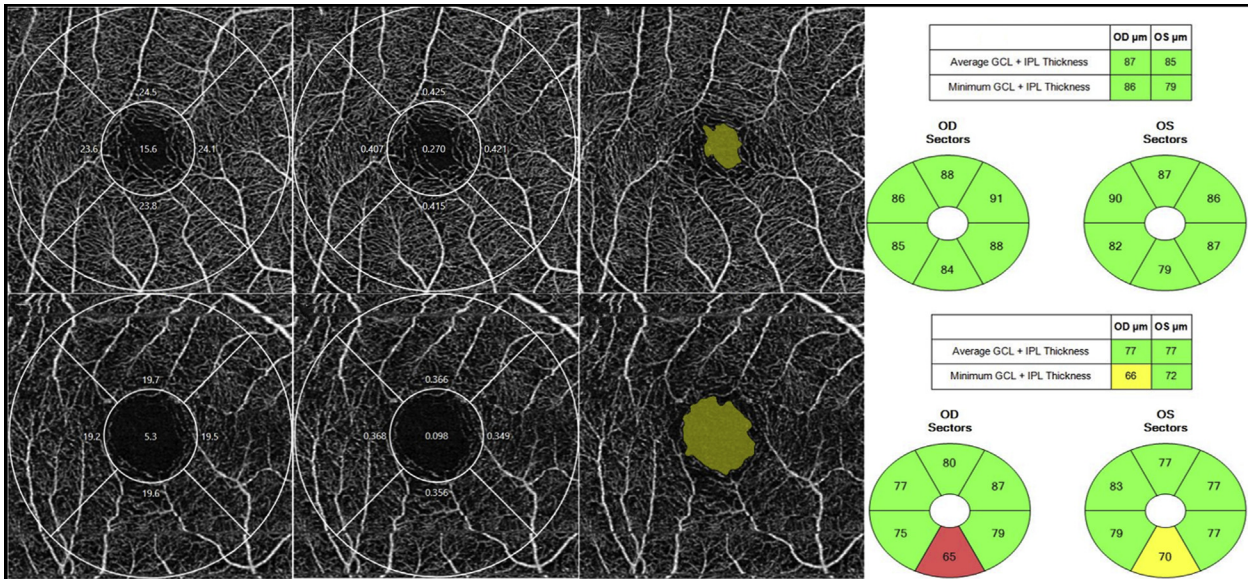

FIGURE 1. A representative optical coherence tomography angiography image (Top and Bottom rows; left, second from left, and right panels) and ganglion cell–inner plexiform layer analyses map (Top right and Bottom right) of a 62-year-old healthy male subject (Top row) and a 64-year-old male patient with hypertension for 10 years who had no other systemic or ocular abnormality (Bottom row). The vessel densities for the total area of the 2 participants were 23.4 mm^{-1} (Top row, left) and 17.9 mm^{-1} (Bottom row, left), and the perfusion densities were 0.401 (Top row, second from left) and 0.331 (Bottom row, second from left), respectively. The automatically detected foveal avascular zone (FAZ) areas were 0.13 mm^2 (Top row, second from right) and 0.43 mm^2 (Bottom row, second from right), respectively.

unit area in a region of measurement; Figure 1, Top, second from left and Bottom, second from left) of the SCP in each subfield were measured automatically. The area and perimeter of the FAZ in the SCP (Figure 1, Top, second from right and Bottom, second from right) were also measured. All OCTA scans were performed by the same experienced examiner, and all scans were reviewed individually by 2 investigators (H.B.L. and M.W.L.) for quality evaluation (ie, loss of fixations, segmentation errors, motion artifacts, and low signal strength [<9]); substandard scans were excluded.

A 512 × 128 macular cube scan and a 200 × 200 optic disc cube scan were also performed to measure macular, GC-IPL, and RNFL thicknesses. The GC-IPL thickness was measured using a ganglion cell analysis algorithm that provided the average of 6 sectors (superotemporal, superior, superonasal, inferonasal, inferior, and inferotemporal [Figure 1, Top right and Bottom right]) of the elliptical annulus centered on the macular area. Then the RNFL thicknesses of the 4 quadrant sectors (superior, inferior, nasal, and temporal) were measured. We excluded results from patients with signal strengths <7 and segmentation errors in the OCT scan.

• **STATISTICAL ANALYSES:** All statistical analyses were performed using SPSS statistical software for Windows, version 21.0 (SPSS, Chicago, Illinois, USA) and Medcalc, version 14.8 (MedCalc, Ostend, Belgium). Snellen BCVA results were converted into the logarithm of the minimum angle of resolution value (logMAR). Continuous variables are presented as the mean ± standard deviation. Differences were considered significant at $P < .05$. Baseline demographics, retinal thickness, and OCTA measurements were compared using 1-way analysis of variance with Bonferroni correction, Student t test, and the χ^2 test. Pearson correlation and univariate linear regression analyses were used to investigate the correlations between inner retinal thickness and retinal vascular metrics. Univariate and multivariate logistic regression analyses were performed to evaluate the determination of factors associated with prolonged hypertension patients, and several factors (BCVA, PD, and FAZ area) with values <1.0 were adjusted (multiplied by 10) for logistic regression analyses.

RESULTS

• **PATIENT CHARACTERISTICS:** This study included a total of 201 participants, including 117 normal controls, 32 in Hypertension Group 1, and 52 in Hypertension Group 2. The mean age of the control group, Hypertension Group 1, and Hypertension Group 2 were 56.94 ± 12.68, 59.38 ± 10.85, and 58.00 ± 7.98 years, respectively, and no significant difference in age was found among the 3 groups

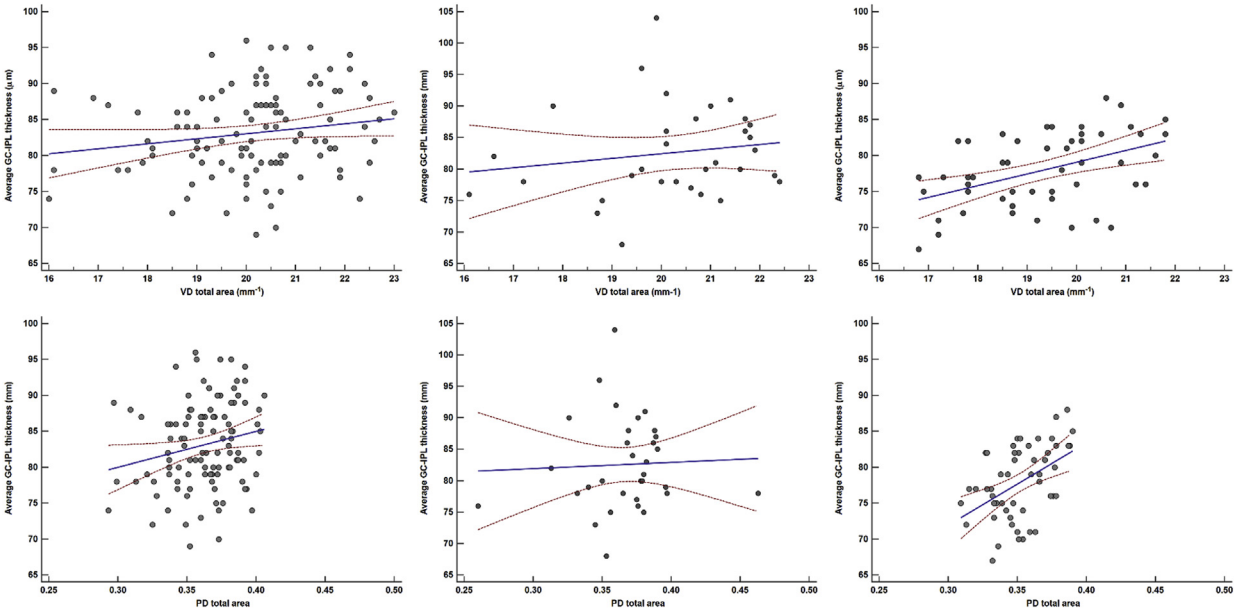

FIGURE 2. Scatterplot and linear regression analyses between the average ganglion cell–inner plexiform layer thickness and vessel density (VD) and perfusion density (PD) in the control group (Top left and Bottom left), Hypertension Group 1 (Top middle and Bottom middle), and Hypertension Group 2 (Top right and Bottom right). VD ($r = 0.450$, $P = .001$) and PD ($r = 0.467$, $P < .001$) in Hypertension Group 2 showed a significant positive correlation with the average GC-IPL thickness, whereas no significant correlation was found in the other groups.

(Table 1). The hypertension duration was 1.95 ± 1.19 years for Hypertension Group 1 and 10.5 ± 4.54 years for Hypertension Group 2 ($P < .001$). There were no significant differences among the 3 groups in the BCVA, spherical equivalent, intraocular pressure, axial length, and various disc parameters, including the cup-to-disc ratio. In antihypertensive medication, angiotensin receptor blocker (75%), β-blocker (3.1%), calcium channel blocker (50.0%), and diuretic (3.1%) were used in Hypertension Group 1, and 73.1%, 1.9%, 67.3%, and 3.8% in Hypertension Group 2, respectively (Supplemental Table 1; Supplemental Material available at AJO.com). The combination therapy was used in 10 (31.3%) patients of Hypertension Group 1 and 24 (46.2%) patients of Hypertension Group 2. There was no significant difference in the antihypertensive medication (all $P > .05$).

• **COMPARISON OF CENTRAL FOVEAL, RETINAL NERVE FIBER LAYER, AND GANGLION CELL–INNER PLEXIFORM LAYER THICKNESSES:** The central foveal thickness of normal controls, Hypertension Group 1, and Hypertension Group 2 were 245.45 ± 18.04 μm, 243.69 ± 20.96 μm, and 241.35 ± 15.78 μm, respectively ($P = .758$; Table 2). The average GC-IPL thicknesses were 83.79 ± 8.80 μm, 80.72 ± 10.85 μm, and 76.79 ± 10.62 μm, respectively, and there were significant differences among groups (all $P < .001$) and all subfields (all $P < .05$). Using post hoc analyses, the GC-IPL thicknesses of all subfields, except the superotemporal area ($P = .062$) in Hypertension Group 2, were significantly lower than those of the normal control group. However, there were no significant differences between the control group and Hypertension Group 1, and between Hypertension Group 1 and Hypertension Group 2, with the exception of the superonasal area ($P = .028$). In RNFL analyses, there was a significant difference in the average ($P = .028$), superior ($P = .031$), and inferior thicknesses ($P = .008$) among the 3 groups. In post hoc analyses, RNFL thicknesses were thinner in Hypertension Group 2 (average [$P = .048$], superior [$P = .041$], and inferior [$P = .006$]) than in the normal control group. No significant differences were observed in other comparisons.

• **COMPARISON OF VESSEL DENSITY, PERFUSION DENSITY, AND FOVEAL AVASCULAR ZONE:** There were significant differences in all of the parameters of OCTA measurements among the 3 groups (Table 3). Using post hoc analyses, the 3-mm total areas of the VD and PD in Hypertension Group 2 were 19.346 ± 1.334 mm^{-1} and 0.353 ± 0.021, respectively, significantly lower than those of Hypertension Group 1 (VD: 20.134 ± 1.811 mm^{-1}, $P = .025$; PD: 0.367 ± 0.033, $P = .043$) and the control group (VD: 20.147 ± 1.522 mm^{-1}, $P = .003$; PD: 0.373 ± 0.025, $P = .048$). In contrast, FAZ area (0.360 ± 0.067) and perimeter (2.595 ± 0.336) were significantly greater in Hypertension Group 2 than in normal controls (FAZ area: 0.318 ± 0.090, $P = .019$; FAZ perimeter: 2.434 ± 0.362, $P = .044$) and

TABLE 1. Demographics and Clinical Characteristics

	Normal Control (N = 117)	Hypertension Group 1 (N = 32)	Hypertension Group 2 (N = 52)	*P* Value
Age (mean ± SD, years)	56.94 ± 12.68	59.38 ± 10.85	58.00 ± 7.98	.136[a]
Sex (male/female)	53/64	11/21	27/25	.292[b]
Smoking, n (%)	19 (16.2)	10 (32.3)	14 (26.7)	.098[b]
HTN duration (mean ± SD, years)	0	1.95 ± 1.19	10.5 ± 4.54	<.001*[a]
Blood pressure				
Systolic pressure (mean ± SD, mm Hg)	119.2 ± 14.4	123.4 ± 14.7	122.6 ± 13.4	.217[a]
Diastolic pressure (mean ± SD, mm Hg)	81.0 ± 7.4	84.2 ± 9.5	82.1 ± 8.2	.098[a]
BCVA (mean ± SD, logMAR)	-0.04 ± 0.07	-0.05 ± 0.07	-0.02 ± 0.06	.108[a]
Spherical equivalent (mean ± SD, diopters)	-0.17 ± 1.46	-0.54 ± 1.27	-0.12 ± 1.16	.236[a]
Intraocular pressure (mean ± SD, mm Hg)	14.80 ± 2.67	15.84 ± 2.50	15.75 ± 2.56	.135[a]
Axial length (mean ± SD, mm)	23.64 ± 0.73	23.59 ± 0.76	23.59 ± 0.54	.993[a]
Rim area (mean ± SD, mm^2)	1.29 ± 0.19	1.35 ± 0.31	1.28 ± 0.24	.310[a]
Disc area (mean ± SD, mm^2)	1.91 ± 0.34	1.99 ± 0.32	1.92 ± 0.33	.485[a]
Cup-to-disc ratio (mean ± SD)	0.53 ± 0.13	0.51 ± 0.19	0.54 ± 0.15	.577[a]
Cup volume (mean ± SD, mm^3)	0.17 ± 0.15	0.20 ± 0.25	0.19 ± 0.15	.386[a]

BCVA = best-corrected visual acuity; HTN = hypertension; LogMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

Numbers marked with an asterisk (*) indicate statistically significant differences at $P < .05$.

[a]The *P* value was determined using 1-way analysis of variance.

[b]The *P* value was obtained using the χ^2 test.

in Hypertension Group 1 (FAZ area: 0.304 ± 0.103, $P = .019$; FAZ perimeter: 2.353 ± 0.438, $P = .011$). There were no significant differences between the control group and Hypertension Group 1.

• **CORRELATION ANALYSES BETWEEN THE INNER RETINAL LAYERS AND MACULAR VESSEL DENSITY:** In Hypertension Group 2, the average thickness of the GC-IPL was significantly correlated with the total areas of the VD (r = 0.450, $P = .001$; Table 4 and Figure 2, Top right) and PD (r = 0.467, $P < .001$; Figure 2, Bottom right), and these trends were also observed in the average thickness of the RNFL (VD: r = 0.314, $P = .027$; PD: r = 0.328, $P = .023$). In the control group and Hypertension Group 1, there was only a weak correlation between the GC-IPL and PD in the normal control group (r = 0.202, $P = .034$; Figure 2, Bottom left).

• **LOGISTIC REGRESSION ANALYSES FOR DETERMINING FACTORS ASSOCIATED WITH PROLONGED HYPERTENSION:** Using univariate logistic regression analyses, the BCVA ($P = .036$), average GC-IPL thickness ($P < .001$), average RNFL thickness ($P = .036$), VD ($P = .001$), PD ($P = .009$), and FAZ area ($P = .018$) were significantly associated with Hypertension Group 2 (Table 5). Multivariate regression analyses including 6 significant variables from univariate analyses showed that only the average GC-IPL thickness was a significant factor, which showed a negative correlation (odds ratio = 0.911, $P = .002$).

DISCUSSION

THE RETINA AND OTHER END ORGANS, SUCH AS THE BRAIN and kidney, have similar vascular structures and physiological properties.[18] Fortunately, retinal vessels are more easily accessible than other end organs, so there have been many studies on the retinal vasculature during hypertension. According to previous studies, hypertension accelerates atherosclerotic change that induces structural modifications of the arterial wall and reduces vessel wall compliance. When BP rises, the retinal blood vessels are changed by vasoconstrictive, sclerotic, exudative, and malignant phases.[19,20] Initially, diffuse and focal vasospasms of the retinal arterioles control the volume of blood received by the retinal capillary bed retinal arteriole, followed by retinal arteriolar narrowing, which reflects vasoconstriction as an autoregulatory response to hypertension.[20] If high BP is chronically sustained, as a next step compression of venules by arterioles, resulting in arteriovenous nicking, occurs, followed by exudative phases caused by disruption of blood-retinal barrier. Retinal hemorrhage, cotton-wool spots, and hard exudates can be observed in this phase, and finally, severe hypertension ultimately leads to a malignant phase with optic disc swelling and macular edema.

Hypertension may be a critical factor in the vascular theory of glaucoma progression; however, its role is controversial. A number of population-based studies have reported that hypertension is a significant risk factor for

TABLE 2. Comparison of Central Macular Thickness, Retinal Nerve Fiber Layer, and Ganglion Cell–Inner Plexiform Layer Thickness Between the Control Group and the Hypertension Group

		Normal Control (μm, Mean ± SD)	Hypertension Group 1 (μm, Mean ± SD)	Hypertension Group 2 (μm, Mean ± SD)	*P* Value[a]	*P* Value[b]	*P* Value[c]	*P* Value[d]
	Central fovea	245.45 ± 18.04	243.69 ± 20.96	241.35 ± 15.78	.758	1.000	0.558	.834
GC-IPL	Average	83.79 ± 8.80	80.72 ± 10.85	76.79 ± 10.62	<.001*	.243	<.001*	.066
	Minimum	79.88 ± 6.67	74.25 ± 15.89	70.92 ± 17.25	<.001*	.051	<.001*	.648
	Superior	84.27 ± 6.82	82.22 ± 11.87	77.77 ± 11.13	<.001*	.626	<.001*	.079
	Superotemporal	81.43 ± 9.52	78.97 ± 11.54	77.64 ± 10.00	.044*	.601	.062	1.000
	Inferotemporal	83.09 ± 6.59	79.41 ± 11.59	77.69 ± 10.62	<.001*	.072	<.001*	1.000
	Inferior	80.94 ± 6.91	78.16 ± 12.16	74.75 ± 9.92	<.001*	.261	<.001*	.237
	Inferonasal	82.84 ± 6.82	81.03 ± 11.30	77.39 ± 10.39	.001*	.765	<.001*	.182
	Superonasal	85.01 ± 6.93	84.84 ± 11.93	79.35 ± 12.25	.001*	1.000	.001*	.028*
RNFL	Average	96.09 ± 12.38	94.41 ± 11.02	91.71 ± 10.56	.028*	1.000	.048*	.911
	Superior	122.03 ± 16.15	120.29 ± 21.53	116.86 ± 19.74	.031*	1.000	.041*	.621
	Temporal	72.33 ± 11.35	71.57 ± 15.74	67.32 ± 12.49	.146	1.000	.151	.432
	Inferior	125.08 ± 12.61	122.61 ± 18.96	117.41 ± 18.20	.008*	1.000	.006*	.281
	Nasal	72.19 ± 10.87	70.04 ± 10.11	69.18 ± 11.29	.446	1.000	.628	.922

GC-IPL = ganglion cell–inner plexiform layer; RNFL = retinal nerve fiber layer.
Numbers marked with an asterisk (*) indicate statistically significant differences at $P < .05$.
[a]The *P* value was obtained using 1-way analysis of variance.
[b]The *P* value was obtained using post hoc tests (Bonferroni) between the normal control and Hypertension Group 1.
[c]The *P* value was obtained using post hoc tests (Bonferroni) between the normal control and Hypertension Group 2.
[d]The *P* value was obtained using post hoc tests (Bonferroni) between Hypertension Group 1 and Hypertension Group 2.

TABLE 3. Comparison of Optical Coherence Tomography Angiography Measurements Between the Control Group and the Hypertension Group

	Normal Control	Hypertension Group 1	Hypertension Group 2	*P* Value[a]	*P* Value[b]	*P* Value[c]	*P* Value[d]
Vessel density (mean ± SD, mm^{-1})							
1-mm center	9.335 ± 2.472	9.788 ± 2.781	8.048 ± 1.904	.002*	.834	.007*	.004*
Average of 4 quadrants	21.539 ± 1.492	21.453 ± 1.839	20.829 ± 1.372	.013*	1.000	.011*	.063
3-mm total area	20.147 ± 1.522	20.134 ± 1.811	19.346 ± 1.334	.004*	1.000	.003*	.025*
Perfusion density (mean ± SD)							
1-mm center	0.162 ± 0.044	0.171 ± 0.046	0.141 ± 0.037	.003*	1.000	.015*	.005*
Average of 4 quadrants	0.388 ± 0.024	0.388 ± 0.029	0.373 ± 0.052	.025*	1.000	.027*	.086
3-mm total area	0.373 ± 0.025	0.367 ± 0.033	0.353 ± 0.021	.020*	1.000	.048*	.043*
Foveal avascular zone							
Area (mean ± SD, mm^2)	0.318 ± 0.090	0.304 ± 0.103	0.360 ± 0.067	.036*	1.000	.019*	.004*
Perimeter (mean ± SD, mm)	2.434 ± 0.362	2.353 ± 0.438	2.595 ± 0.336	.008*	.659	.044*	.011*

SD = standard deviation.
Numbers marked with an asterisk (*) indicate statistically significant differences at $P < .05$.
[a]The *P* value was obtained using 1-way analysis of variance.
[b]The *P* value was obtained using post hoc tests (Bonferroni) between the normal control group and Hypertension Group 1.
[c]The *P* value was obtained using post hoc tests (Bonferroni) between the normal control group and Hypertension Group 2.
[d]The *P* value was obtained using post hoc tests (Bonferroni) between Hypertension Group 1 and Hypertension Group 2.

glaucoma.[21–24] In meta-analyses, it has been reported that hypertension was closely related with the progression of open-angle glaucoma.[25,26] On the other hand, several population-based studies found no significant association.[27,28] Decreased ocular perfusion pressure (OPP) is strongly associated with an increased prevalence of open-angle glaucoma. However, elevated BP may theoretically increase the OPP.[9,24] In addition, several studies

TABLE 4. Correlation Analyses Between Inner Retinal Layers and Optical Coherence Tomography Angiography Measurements

	Normal Control			Hypertension Group 1			Hypertension Group 2		
	r	β ± SE	*P* Value	r	β ± SE	*P* Value	r	β ± SE	*P* Value
GC-IPL									
VD 3-mm total area	0.172	0.695 ± 0.381	.071	0.307	1.839 ± 1.041	.087	0.450	1.627 ± 0.456	.001*
PD 3-mm total area	0.202	49.807 ± 23.178	.034*	0.151	49.648 ± 59.409	.410	0.467	114.515 ± 30.650	<.001*
RNFL									
VD 3-mm total area	0.011	-0.091 ± 0.798	.909	0.152	0.925 ± 1.098	.406	0.314	2.289 ± 1.000	.027*
PD 3-mm total area	0.013	-6.666 ± 48.778	.892	0.113	37.898 ± 60.678	.537	0.328	152.838 ± 65.009	.023*

GC-IPL = ganglion cell–inner plexiform layer; PD = perfusion density; RNFL = retinal nerve fiber layer; SE = standard error; VD = vessel density.

Numbers marked with an asterisk (*) indicate statistically significant differences at $P < .05$.

have reported that BP showed a significant positive correlation with IOP,[29,30] whereas others did not.[31,32] Although it has not been clearly established how hypertension affects the optic nerve system when related to glaucoma, it is believed that both conditions are closely correlated.

Several studies have measured retinal vessel diameters to evaluate retinal arteriole narrowing, one of the early signs of hypertensive retinopathy. The results have been useful for predicting the prognoses of various diseases associated with hypertension.[33–35] However, the methods these studies employed are semiautomatic, and specialized software and technicians are required for vascular analyses, which may not be clinically available. Schuster and associates reported that the arteriovenous ratio measured using OCT is significantly correlated with BP.[36] This method also measures the retinal vessel diameter manually, not automatically, in line scan images, so it is difficult to obtain the actual values of the vertical cross sections.

The OCTA used in this study is currently widely used, and we could obtain information on retinal microcirculation both quickly and easily. In this study, the inner retinal layers of patients with prolonged hypertension were significantly thinner than those of normal controls. In addition, VD and PD were significantly decreased in Hypertension Group 2, and FAZ tended to be larger. Taking into account the significant correlation between the inner retinal layer thickness and microvascular metrics, it is suggested that losses in the GC-IPL and peripapillary RNFL in hypertensive patients may be related to retinal microcirculation.

In this study, there were no differences in BP among the 3 groups, and there was no significant correlation between BP and vascular metrics (all $P > .05$; data not shown). Considering previous reports that past BP and transient changes in BP, as well as current BP, are associated with arterial narrowing,[33,37–39] the decrease in VD and PD observed in our study might have been associated with retinal arteriolar narrowing caused by the previous BP or transient changes in BP, rather than the current BP. These changes caused retinal microcirculational disturbances, which suggests that retinal ischemia may have affected the retinal thickness. Inner retinal thinning was mainly observed in patients in Hypertension Group 2, although BP was well controlled, and the longer the duration of the disease, the more vascular events accumulated, resulting in microvascular changes.

Hypertension is a significant risk factor for glaucoma, and GC-IPL and RNFL thinning in this study might be a change associated with glaucoma progression. However, considering that all hypertensive patients had healthy discs, no increased cup-to-disc ratio, and no RNFL defects, we assumed that the reduction in GC-IPL and RNFL thicknesses in patients with hypertension might have been influenced by factors other than glaucoma progression. Akay and associates[40] reported that the ganglion cell complex is significantly lower in hypertensive patients than in normal controls, and that its thickness could be a sensitive parameter in the early detection of retinal changes. Hypertensive patients included in this study were young (23.8 ± 2.8 years) and had no abnormal ocular findings. In our previous study,[12] we found that the GC-IPL and RNFL in patients with hypertension lasting >10 years were significantly thinner than in controls. Hypertensive patients also had no glaucomatous findings. Taken together, these data suggest that not only glaucoma progression but also retinal microcirculational disorders caused by hypertension may play a significant role in inner retinal thinning in hypertensive patients.

In this study, the thickness decrease was more prominent in the GC-IPL than in the peripapillary RNFL. Although it

TABLE 5. Univariate and Multivariate Logistic Regression Analyses for Determining the Factors Associated With Prolonged Hypertension

	Univariate Analyses			Multivariate Analyses		
Factors	B	OR (95% Confidence Interval)	*P* Value	B	OR (95% Confidence Interval)	*P* Value
Age	0.021	1.021 (0.991–1.052)				
Sex (0 = male, 1 = female)	0.357	1.428 (0.756–2.699)	.272			
BCVA	0.555	1.742 (1.037–2.926)	.036*	0.269	1.003 (0.970–1.037)	.358
Spherical equivalent	0.042	1.043 (0.822–1.322)	.730			
Intraocular pressure	0.118	1.125 (0.993–1.274)	.063			
Axial length	-0.023	0.977 (0.602–1.586)	.925			
Central foveal thickness	-0.018	0.982 (0.965–1.000)	.060			
Average GC-IPL thickness	-0.108	0.897 (0.853–0.944)	<.001*	-0.093	0.911 (0.859–0.967)	.002*
Average RNFL thickness	-0.030	0.970 (0.943–0.998)	.036*	0.003	1.003 (0.970–1.037)	.878
VD (3-mm total area)	-0.350	0.704 (0.568–0.874)	.001*	-0.242	0.785 (0.488–1.263)	.318
PD (3-mm total area)	-1.750	0.174 (0.047–0.641)	.009*	0.539	1.714 (0.107–27.499)	.704
FAZ area	0.466	1.593 (1.081–2.347)	.018*	0.348	1.416 (0.927–2.165)	.108

BCVA = best-corrected visual acuity; FAZ = foveal avascular zone; GC-IPL = ganglion cell–inner plexiform layer; OR = odds ratio; PD = perfusion density; RNFL = retinal nerve fiber layer; VD = vessel density.

Numbers marked with an asterisk (*) indicate statistically significant differences at $P < .05$.

is difficult to definitively explain, the expected mechanism may be as follows. First, the ganglion cell layer is highly sensitive to acute, transient, and mild systemic hypoxic stress.[41] Second, the ganglion cell bodies in the macular region are multilayered and 10- to 20-fold thicker than their axons.[42] Hence, changes in the ganglion cell layer may be easier to detect in the macular region than in the peripapillary area.

This study had some limitations. First, it had a retrospective design, which may have involved selection bias. Second, there was not enough information about the systemic status of the included participants, and it was difficult to analyze how the decreased measurements in the OCTA were associated with other systemic diseases caused by hypertension. Third, because the BP might have been increased before hypertension diagnosis, the actual high blood pressure period could be longer than the hypertension treatment period. Fourth, various factors, including diastolic BP reduction, nocturnal BP dip, reduced BP following antihypertensive therapy, and impair vascular autoregulation such as migraine and Flammer syndrome,[43] may affect retinal perfusion and inner retina. Finally, the area of the GC-IPL scan and the OCTA scan were not exactly the same. This discrepancy might have some effect on the results. Additional prospective, well-designed studies are needed to overcome these limitations.

In conclusion, we confirmed inner retinal layer thinning, particularly in the GC-IPL, in patients with hypertension lasting more than 5 years. Hypertensive patients had decreased retinal blood flow, which was significantly correlated with injury of the inner retinal layer. This is the first study to demonstrate an association between injuries of the retinal ganglion cell layer and retinal microcirculational disorders. Therefore, our results will be useful in analyses of GC-IPL thickness in patients with various ocular diseases such as glaucoma and neuroretinal diseases. The effects of hypertension on the GC-IPL should also be considered.

FUNDING/SUPPORT: NO FUNDING OR GRANT SUPPORT. FINANCIAL DISCLOSURES: THE FOLLOWING AUTHORS HAVE NO financial disclosures: Hyung Bin Lim, Min Woo Lee, Jae Hyeong Park, Kyeungmin Kim, Young Joon Jo, and Jung Yeul Kim. All authors attest that they meet the current ICMJE criteria for authorship.

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