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The Correlation of Retinal Nerve Fiber Layer Thickness With Blood Pressure in a Chinese Hypertensive Population

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Abstract: To investigate the association between retinal nerve fiber layer (RNFL) thickness and blood pressure (BP) in subjects with systemic hypertension.

Subjects with systemic hypertension on anti-hypertensive medications were screened by fundus photography and referred for glaucoma work-up if there was enlarged vertical cup-to-disc (VCDR) ratio $\geq$0.6, VCDR asymmetry $\geq$0.2, or optic disc hemorrhage. Workup included a complete ophthalmological examination, Humphrey visual field test, and RNFL thickness measurement by optical coherence tomography. The intraocular pressure (IOP) and RNFL thicknesses (global and quadrant) were averaged from both eyes and the means were correlated with: the systolic BP (SBP), diastolic BP (DBP), and mean arterial pressure (MAP) using Pearson correlation.

Among 4000 screened hypertensive subjects, 133 were referred for glaucoma workup and 110 completed the workup. Of the 4000 screened subjects, 1.3% had glaucoma (0.9% had normal tension glaucoma [NTG], 0.2% had primary open angle glaucoma, and 0.2% had primary angle closure glaucoma), whereas 0.3% were NTG suspects. The SBP was negatively correlated with the mean superior RNFL thickness ($P = 0.01$). The DBP was negatively correlated with the mean global ($P = 0.03$), superior ($P = 0.02$), and nasal ($P = 0.003$) RNFL thickness. The MAP was negatively correlated with the mean global ($P = 0.01$), superior ($P = 0.002$), and nasal ($P = 0.004$) RNFL thickness while positively correlated with the mean IOP ($P = 0.02$).

In medically treated hypertensive subjects, glaucoma was present in 1.3%, with NTG being most prevalent. MAP control may help with IOP lowering and RNFL preservation, although future prospective studies will be needed.

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Abbreviations: BP = blood pressure, DBP = diastolic blood pressure, ETDRS = Early Treatment Diabetic Retinopathy Study, HT = hypertension, IOP = intraocular pressure, MAP = mean arterial pressure, NTG = normal tension glaucoma, PACG = primary angle closure glaucoma, POAG = primary open angle glaucoma, RNFL = retinal nerve fiber layer, SBP = systolic blood pressure, VCDR = vertical cup-to-disc ratio.

Glaucoma is a chronic, progressive and irreversible optic neuropathy with characteristic anatomical and structural defects due to loss of the retinal ganglion cells. Loss of the retinal nerve fiber layer (RNFL) may precede visual field changes.[1,2] Various studies have demonstrated that up to 40–50% of the retinal ganglion cells need to be lost before visual field defects are observed in standard automated perimetry, which is still considered to be one of the gold standard investigations for glaucoma.[3,4] Assessment of RNFL thickness, on the other hand, is an objective test that has a high degree of correlation with visual field defects but at the same time able to detect earlier, pre-perimetric disease.[5,6]

Intraocular pressure (IOP) is still the most important modifiable risk factor of glaucoma progression. Vascular risk factors such as systemic hypertension, ocular perfusion pressure, hypercoagulability, carotid artery disease, and vasospasm have been extensively studied and it has been demonstrated that ocular hypoperfusion and systemic blood pressure play a vital role in the pathogenesis of glaucoma.[7–13] Some studies have demonstrated a positive association between systemic hypertension (HT) and glaucoma,[14–18] whereas others have demonstrated no significant association between the 2 entities.[19,20]

To our knowledge, very few studies have examined the association between RNFL thickness and BP.[21,22] The purpose of our study was to determine association between RNFL thickness with systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in subjects with medically treated systemic HT.

PATIENTS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and no patients' personal data were disclosed in the study. Study approval was obtained from the institutional review board of the Hospital Authority of Hong Kong. The authors declare no financial or proprietary interests. This was a non-funded study.

In this prospective population-based study, patients with systemic HT were invited by family physicians at 2 primary care outpatient clinics to join the Risk Assessment and Management Programme. Informed consent was taken from all the patients. The assessment included BP measurement, blood tests for blood glucose, renal and liver function, lipid profile, urine test, electrocardiography, and ophthalmological examination as described below. The patient was allowed to rest for at least 15 minutes before the SBP and DBP (mmHg) were measured by

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an automated machine (Blood pressure monitor TM-2655P, Biospace, Japan). If the SBP was >170 mmHg or the DBP was >90 mmHg, a repeated measurement was performed.

Ophthalmological examination included: pin-hole visual acuity by "Early Treatment Diabetic Retinopathy Study" (ETDRS) chart, slit lamp biomicroscopy, and fundus photography after pupil dilatation with Mydriacyl (Tropicamide) 1% eye drops (SA Alcon-Couvreur NV, Belgium). Digital, color, non-stereoscopic retinal photographs were captured by fundus camera (Non-mydriatric Auto Fundus Camera AFC-230, NIDEK, Japan); 2 photographs were taken for each eye, one with macula-centered and the other with disc-centered. The fundus photographs were transferred from the outpatient clinic to the grading center using Optomize software (version 1.1) (Digital Healthcare, Cambridge, United Kingdom) and Health Level 7 (HL7) standard protocol (HL7 Inc, Ann Arbor, MI). The photographs were graded for the severity of hypertensive retinopathy by 2 trained optometrists using a computer monitor with resolution of 1024×768 pixels. In the presence of other eye diseases, such as retinal vein occlusion, increased vertical cup-to-disc ratio (VCDR), age-related macular degeneration, or other macular pathologies, the photographs were further graded by an ophthalmologist. Patients with VCDR $\geq$0.6, VCDR asymmetry $\geq$0.2, and/or disc hemorrhage were referred to an ophthalmology specialist clinic for detailed workup for glaucoma and concomitant ophthalmological diseases were treated accordingly. Subjects referred to the ophthalmology clinic underwent a complete ophthalmological examination to determine the best corrected visual acuity, intra-ocular pressure (IOP) measurement with Goldmann applanation tonometry, central corneal thickness measurement with a pachymeter (Quantel Medical, 63039 Clermonte-Ferrand cedex 2, France), slit lamp examination, gonioscopy, and fundus examination using a 78 Dioptre (D) or 90D lens after pharmacological pupil dilatation. Subjects also underwent automated visual field testing using the 24–2 standard Swedish Interactive Threshold Algorithm of the Humphrey Visual field Analyzer II (Carl Zeiss Meditec Inc., Dublin, CA) (HVF). The RNFL was measured using a Spectral-domain Optical Coherence Tomography (Heidelberg Spectralis; Heidelberg software version 5.3.3.0, Eye Explorer software 1.6.4.0, Heidelberg Engineering GmbH, Heidelberg, Germany).

The diagnosis of glaucoma was based on the criteria and guidelines of the International Society for Geographical and Epidemiological Ophthalmology.[23]

The inclusion criteria included all consenting adults with systemic HT who completed the BP measurement and ophthalmological examination and investigations as required. Subjects were excluded if they defaulted any of the glaucoma investigations.

Definitions

1 Primary angle closure glaucoma (PACG): Presence of glaucomatous optic neuropathy plus $\geq$270 degree peripheral anterior synechiae or appositional closure less than grade 2 on gonioscopy according to the Shaffer grading system.
2 Primary open angle glaucoma (POAG): Presence of glaucomatous optic neuropathy plus $\geq$270 degree grade 2 or above on gonioscopy according to the Shaffer grading system with IOP >21 mmHg on at least 2 clinic visits.
3 Normal tension glaucoma (NTG): Presence of glaucomatous optic neuropathy plus IOP $\leq$21 mmHg on at least 2 clinic visits and open angle configuration.
4 NTG suspect: Same as for NTG with evidence of RNFL thinning on OCT but unreliable HVF on 2 occasions or absence of corresponding HVF defects.
5 For the diagnosis of glaucoma: RNFL parameters were defined as presence of RNFL thinning in the global and/or in any of the 4 quadrants based on a yellow or red-colored map as compared with the normative database (which resembles a RNFL thickness below the 95th percentile of normal). In addition to the RNFL thinning, there must be presence of corresponding defects seen on the HVF according to Hodapp-Parrish-Anderson's criteria.[24] An elevation of IOP was not required for the diagnosis of glaucoma.
6 The mean arterial blood pressure (MAP): Calculated using the formula below where MAP equals to two-thirds of the DBP plus one-third of the SBP.

$$MAP \simeq \frac{(2 \times DBP) + SBP}{3}$$

The RNFL thickness (global, superior, nasal, inferior, and temporal) and IOP between the right and left eyes were averaged for each individual to produce an average RNFL and IOP in microns (μm) and mmHg, respectively.

Statistics

The Kolmogorov–Smirnov test was used to determine normality of the data. The Pearson correlation coefficient was used to analyze the following:

1. SBP with averaged RNFL (global, superior, nasal, inferior, and temporal) and averaged IOP.
2. DBP with averaged RNFL (global, superior, nasal, inferior, and temporal) and averaged IOP.
3. MAP with averaged RNFL (global, superior, nasal, inferior and temporal) and averaged IOP.

Differences between groups were tested using 2-sample *t* tests for continuous variables and the χ^2 test for categorical variables. P value <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc, IBM SPSS statistics, NY) version 19.

RESULTS

During the study period, 4000 subjects with primary systemic HT being treated with anti-hypertensive medications were screened for retinal abnormalities using fundus photography at 2 primary care outpatient clinics in Hong Kong. Among these 4000 subjects, 133 were identified as glaucoma suspects based on the presence of enlarged or asymmetrical VCDR and/or disc hemorrhage. These subjects were referred to the specialist ophthalmology clinic of an university hospital for further investigations. Of these 133 subjects, 110 subjects completed a full ophthalmological examination including HVF and RNFL thickness assessment by OCT, whereas 23 defaulted the referral or investigation appointments. The patient demographics are summarized in Table 1.

Of these 110 subjects, 46 were confirmed not to have glaucoma after full workup. Among the remaining 64 patients, 36 (56.3%) had NTG, 8 (12.5%) had POAG, 8 (12.5%) had PACG, and 12 (18.7%) were NTG suspects. The prevalence of glaucoma among the entire cohort of 3977 subjects (after excluding the 23 patients who defaulted the referral or investigation appointments) was as follows: NTG (0.9%), POAG (0.2%), PACG (0.2%), and NTG suspects (0.3%) (Fig. 1).

TABLE 1. Demographic Characteristics of Subject Who Completed Detailed Ophthalmological Examination

No. of patients	110
Sex (M: F)	1.4:1 (64 males, 46 females)
Age, (years)	65.1 ± 9.5 (range:43–85)
Mean systolic BP, (mmHg) (with anti-hypertensive medications)	139.1 ± 15.4 (range:111–181)
Mean diastolic BP, (mmHg) (with anti-hypertensive medications)	80.2 ± 10.9 (range:53–110)
Mean arterial pressure, (mmHg) (with anti-hypertensive medications)	99.8 ± 10.8 (range:74–126)
Mean vertical cup-disc ratio	0.7 ± 0.12
Mean intraocular pressure, (mmHg)	17.4 ± 0.3 (range:12–24)
Mean retinal nerve fiber layer, (μm)	82.3 ± 16.6 μm (range:33.5–111)
Mean MD on Humphrey Visual field, (dB)	−4.20 ± 5.09 (range: +0.50 to −27.8)
Mean PSD on Humphrey Visual field, (dB)	3.4 ± 2.65 (range:1.10–13.42)
Mean Snellen visual acuity	0.68 (range:0.2–1.0)
Mean Central Corneal Thickness, (μm)	544 ± 34.05 (range:479–632)

MD = mean deviation, PSD = pattern standard deviation.

The SBP was negatively correlated with the mean superior RNFL thickness ($r = -0.3$, $P = 0.01$). The DBP was negatively correlated with the mean global ($r = -0.2$, $P = 0.03$), superior ($r = -0.2$, $P = 0.02$), and nasal ($r = -0.3$, $P = 0.003$) RNFL thicknesses. The MAP was negatively correlated with: the mean global ($r = -0.3$, $P = 0.01$), superior ($r = -0.3$, $P = 0.002$), and nasal ($r = -0.3$, $P = 0.004$) RNFL thicknesses while positively correlated with the averaged IOP ($r = 0.2$, $P = 0.02$). There were no significant correlations of the SBP or DBP with IOP (all $P \geq 0.3$) (Table 2).

There was a significant linear relationship between MAP versus the average global RNFL thickness ($r^2 = 0.06$, $P = 0.02$) and averaged IOP ($r^2 = 0.06$, $P = 0.02$) (Figs. 2 and 3).

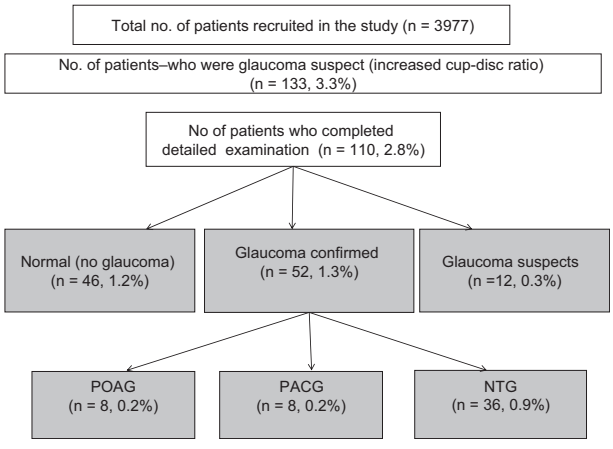

FIGURE 1. Schematic diagram for the inclusion of subjects.

Figure 4 depicts a typical fundus photograph of the optic discs showing an increased VCDR with corresponding RNFL thinning on OCT.

DISCUSSION

Autoregulation is an important blood flow regulatory mechanism, which is present in body tissues including the retina and optic nerve head.[9,10] It helps to keep the blood flow relatively constant during changes in perfusion pressure.[9] If the perfusion pressure is above or below a critical range, autoregulation malfunctions, making tissues vulnerable to ischemia. The perfusion pressure depends on BP; thus, an excessive increase or decrease in BP can cause breakdown of the autoregulation system.[9] Hypertension can cause changes in arterioles such as vasospasm, arteriolosclerosis, vasodilation, or vasoconstriction caused by angiotensin. All of these changes can interfere with autoregulation.

Nocturnal arterial hypotension plays an important role in perfusion of the optic nerve. Studies have shown that low BP impairs blood flow to the optic disc and induces glaucomatous damage.[8,9] The relationship between BP and glaucoma is complex. Several studies have shown J-shaped association between BP and POAG.[25] Both hypertension and hypotension are risk factors for glaucoma.[25]A recent meta-analysis on the association of BP and glaucoma has shown stronger associations between hypertension and POAG in cross-sectional studies as compared with case–control and longitudinal studies.[18] In our cross-sectional study, a higher SBP, DBP, and MAP were associated with thinner RNFL thicknesses. Our findings were in agreement with the Los Angeles Latino Eye Study, which reported that higher prevalence of open angle glaucoma with higher SBP and MAP.[25] Our findings were also in agreement with Blue Mountains Eye study, in which, Mitchell et al[16] also reported that subjects treated for HT and those with poorer control of HT had a higher risk of open angle glaucoma. Systemic HT, even when treated with anti-hypertensive medications, has been shown to be a risk factor for progressive RNFL thinning in subjects with glaucoma.[21] Our findings of a higher DBP inducing greater RNFL thinning were in contrast to those reported by McGlynn et al[26] who reported that a lower DBP was associated with more progressive RNFL loss (OR = 0.2 per 10 mmHg, 95% CI 0.1–0.6, $P < 0.006$). As previously mentioned, from the Los Angeles Latino Eye Study, it was demonstrated that the relationship between DBP and glaucoma prevalence is in a ''U-shape'' signifying that extremes of DBP (too high or too low) were detrimental for glaucoma since a high DBP can cause vascular dysregulation, whereas a low DBP can result in a low ocular perfusion pressure.[25] However, we could not have observed a ''U-shaped'' relationship to BP in our study because we only investigated hypertensive patients.

We also found that the MAP was positively correlated with IOP, which was consistent with the Beijing Eye Study that reported a drop in MAP associated with a drop in IOP.[27] Various studies have documented the significance of perfusion pressure in the pathogenesis of glaucomatous optic nerve damage.[12,28–30] Previous studies have shown the significant association between RNFL thinning and reduced blood flow in patients with glaucoma.[12,28] It has been shown that reducing the ocular perfusion pressure by prone posturing even for 120 min during spinal surgery resulted in RNFL thinning in the inferior and nasal RNFL quadrants.[31] Likewise, Tielsh et al[28] showed that lower diastolic perfusion pressure (DBP minus IOP) was associated with POAG.

TABLE 2. Pearson Correlation of Blood Pressure With Averaged RNFL and IOP From Both Eyes

	Averaged RNFL Thickness					
	Global	**Superior**	**Nasal**	**Inferior**	**Temporal**	**Averaged IOP**
SBP	$r=-0.2$	$r=-0.3$	$r=-0.1$	$r=-0.05$	$r=-0.004$	$r=-0.08$
	$P=0.7$	$P=0.01^*$	$P=0.8$	$P=0.7$	$P=0.9$	$P=0.5$
DBP	$r=-0.2$	$r=-0.2$	$r=-0.3$	$r=-0.1$	$r=0.0$	$r=0.08$
	$P=0.03^*$	$P=0.02^*$	$P=0.003^*$	$P=1.0$	$P=0.4$	$P=0.4$
MAP	$r=-0.3$	$r=-0.3$	$r=-0.3$	$r=-0.13$	$r=-0.03$	$r=0.2$
	$P=0.01^*$	$P=0.002^*$	$P=0.004^*$	$P=0.2$	$P=0.6$	$P=0.02^*$

DBP = diastolic blood pressure, IOP = intraocular pressure, MAP = mean arterial blood pressure, RNFL = retinal nerve fiber layer, SBP = systolic blood pressure.
* Statistically significant.

In our study, of the 3977 systemic HT subjects that completed the study, 1.3% had confirmed glaucoma and 0.3% were glaucoma suspects. The prevalence of NTG was 0.9%, POAG was 0.2%, and PACG was 0.2%. This was lower than the figures reported in other population studies such as the Beijing Eye study that reported a prevalence of 2.6% for POAG and 1% for PACG.[27] The overall prevalence of open angle glaucoma in the United States was 1.86%, whereas in the Rotterdam Study, it was 0.8%.[32,33] However, we cannot directly compare our findings with these general population studies, as we have specifically selected a population of medically treated HT subjects for screening. However, the Blue mountains eye study examined 3654 subjects to determine the association between HT and open angle glaucoma.[16] It was found that subjects with poorly controlled HT had a higher prevalence of glaucoma (5.4%) compared with normotensive subjects (1.9%),[15] which was in line with the glaucoma prevalence of 1.3% reported in our study, as in our population, the BP of subjects was medically controlled to fall within a normal range (mean BP = 139.1 ± 15.4 /80.2 ± 10.9 mmHg). The higher proportion of NTG was expected, as this disease involves not only an IOP-dependent component but also a hypoperfusion component, which can be caused by HT either directly due to vascular dysregulation or indirectly by excessive hypotension from overtreatment.[17]

Glaucoma being a broad-spectrum disease rather than a single-disease entity encompasses chronic neurodegenerative changes in the optic nerve and brain. Recently, some studies have focused on the cellular and molecular mechanisms of glaucoma.[34] A recent study mentioned the role of the dopaminergic receptors in glaucoma.[35] Dopamine (DA) is an organic chemical in catecholamine family released from post-ganglionic nerve fibers of the superior cervical dopaminergic ganglion in the aqueous humor. DA acts by binding to 5 different receptors (DA_1, DA_2, DA_3, DA_4, and DA_5). DA_1-like receptors include DA_1 and DA_5, whereas DA_2-like receptors include DA_2, DA_3, and DA_4.[35] The stimulation of DA_1 or DA_1 agonists stimulates the production of aqueous humor and increases IOP, whereas stimulation of DA_2 and DA_3 receptors suppresses aqueous production and reduces IOP. DA is also an important regulator of systemic BP.[36] At present, the direct correlation between dopamine receptors with systemic HT and glaucoma is not well understood, but the importance of DA receptors (DA_2 and DA_3-agonists) in reducing IOP is being recognized.[35]

Scarsella et al[37] demonstrated in rat eyes the importance of IOP and blood flow in glaucoma. In their study, they demonstrated that an experimentally induced episode of acute IOP rise resulted in ischemic damage to optic nerve in the form of

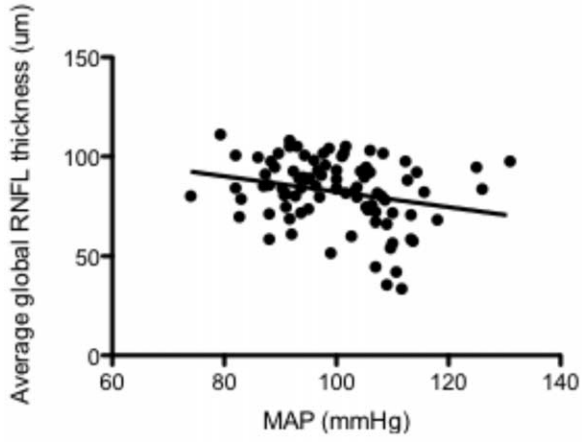

FIGURE 2. Linear relationship between MAP and averaged global RNFL thickness of both eyes. MAP = mean arterial blood pressure, RNFL = retinal nerve fiber layer.

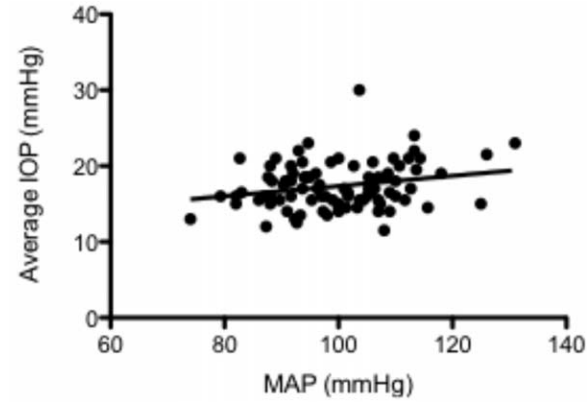

FIGURE 3. Linear relationship between MAP and averaged IOP of both eyes. IOP = intraocular pressure, MAP = mean arterial blood pressure.

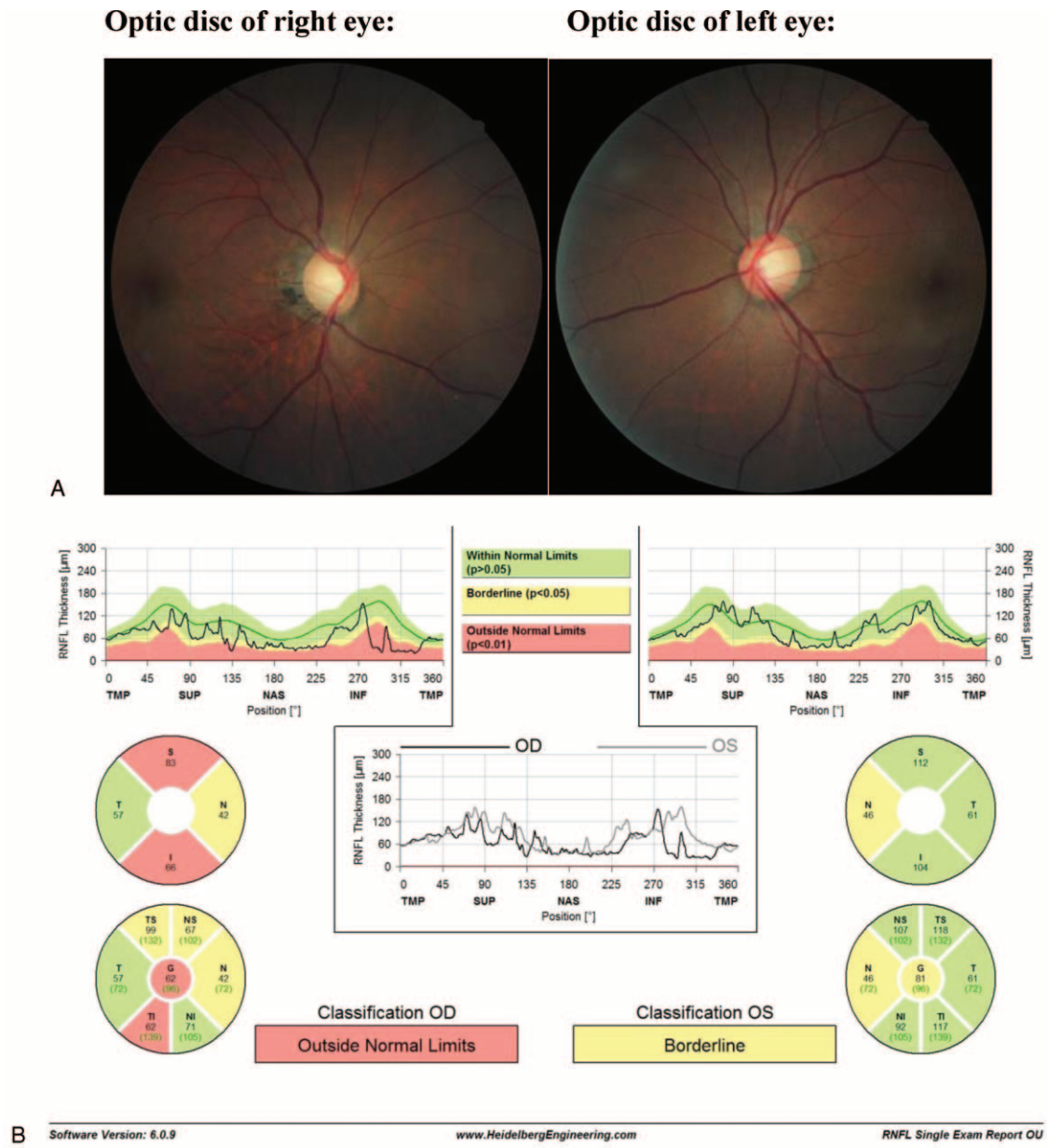

FIGURE 4. (A) Fundus photographs of right and left eyes of a subject with systemic hypertension with increased cup-to-disc ratio. (B) OCT disc images of right and left eyes of the subject in FIGURE 4A showing corresponding retinal nerve fiber layer thinning.

vascular changes (enlargement and branching of radial venules and arteriole thickening) along with increased pro-angiogenic factor vascular endothelial growth factor expression. They also demonstrated that an acute rise of IOP could arrest the axonal flow of neuronal mediators.[37] A better understanding of the relationships between IOP, glia, vessels, and neurons may deepen our understanding on the progression of glaucoma. Thus, vascular supply to the optic nerve reflected by systemic BP and IOP both play a vital role in glaucomatous damage.

There were certain limitations in our study. First, due to logistical constraints, BP was measured during the clinic visit only, and therefore diurnal variation could not be accounted for and BP fluctuations and nocturnal dips were not measured. Second, IOP was also measured only during clinic visits and diurnal IOP variation was not accounted for. Third, subjects were identified on the basis of an increased VCDR $\geq$0.6, and the fundus photographs were non-stereoscopic; therefore, a small proportion of patients who may have had glaucoma but with VCDR $<$0.6 may have been undiagnosed and not included in this study. Fourth, we did not include factors such as age, family history of glaucoma, and history of diabetes in our subjects, which could have been additional risk factors for glaucoma. Fifth, we did not examine the impact of the different types of systemic antihypertensive medications. Sixth, the cross-sectional nature of our study did not enable us to determine the causal relationship between systemic HT and RNFL thinning. The findings of this study may not be generalizable for other hypertensive populations or to populations without hypertension.

In conclusion, in a population of 4000 medically treated systemic HT subjects, 1.3% was confirmed to have glaucoma with NTG being the most prevalent glaucoma subtype. A higher MAP was associated with a higher IOP and thinner global RNFL thickness. A higher DBP was also associated with a thinner global RNFL. Blood pressure optimizations may be of use in IOP control and RNFL preservation, although larger prospective trials following the subjects over time are warranted to establish the causal associations.

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