

Prospective Pilot Clinical Study of Noninvasive Cerebrovascular Autoregulation Monitoring in Open-Angle Glaucoma Patients and Healthy Subjects

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Purpose: To analyze the cerebrovascular autoregulation (CA) dynamics in patients with normal-tension glaucoma (NTG) and high-tension glaucoma (HTG) as well as healthy subjects using noninvasive ultrasound technologies for the first time.

Methods: The CA status of 10 patients with NTG, 8 patients with HTG, and 10 healthy subjects was assessed, using an innovative noninvasive ultrasonic technique, based on intracranial blood volume slow-wave measurements. Identified in each participant were intraocular pressure, ocular perfusion pressure, and CA-related parameter volumetric reactivity index (VRx), as well as the duration and doses of the longest cerebral autoregulation impairment (LCAI). In addition, we calculated the associations of these parameters with patients' diagnoses.

Results: The VRx value, the LCAI dose, and duration in healthy subjects were significantly lower than in patients with NTG ($P < 0.05$). However, no significant differences were noted in these parameters between healthy subjects and HTG and between NTG and HTG groups.

Conclusions: NTG is associated with the disturbed cerebral blood flow and could be diagnosed by performing noninvasive CA assessments.

Translational Relevance: The VRx monitoring method can be applied to a wider range of patient groups, especially patients with normal-tension glaucoma.

Introduction

Glaucoma is a multifactorial, progressive neurodegenerative disorder that results in optic nerve head damage and visual field loss. Patients with high range intraocular pressure (IOP) can

develop glaucoma. However, patients with normal-range IOP can also develop glaucomatous optic neuropathy. Primary open-angle glaucoma is the most common type of glaucoma worldwide and can be clinically classified into two subgroups: high-tension glaucoma (HTG), in which IOP is greater than 21 mm Hg, and normal-tension

glaucoma (NTG), in which IOP is within the normal range.¹

The pathogenesis of glaucoma is not fully understood. However, several theories have been put forward such as mechanical and vascular theories to explain the pathogenesis of glaucoma.²⁻⁴ The mechanical theory considers glaucomatous optic neuropathy to be a direct consequence of IOP, which damages the lamina cribrosa and neural axons.^{5,6} However, the vascular theory considers glaucomatous optic neuropathy as a consequence of low perfusion pressure of the optic nerve.^{3,7} The decreased optic nerve perfusion may result from vascular failure that includes vasospasms, small vessel disease, and autoregulatory dysfunction.^{8,9}

However, explanations of NTG are still controversial. Studies believe that glaucoma causes dysfunction of the autoregulation of the ocular blood flow.^{10,11} Typically, the ocular blood flow autoregulation is characterized by local vascular constriction or dilation, which makes vascular resistance reciprocally increase or decrease, thereby keeping a relatively constant temperature for ocular and constant pressure for retinal perfusion.^{10,11}

Other studies suggest that disturbed ocular blood flow is a major factor associated with the pathogenesis of NTG.^{6,12} Disturbance in the autoregulatory pathway may decrease perfusion and lead to ischemic damage of the optic nerve or retinal ganglion cells.¹⁰ Although several methods have been put forward, no single vascular indicator can completely evaluate ocular blood flow.¹³

Vascular dysregulation in glaucoma is one of the results of impaired cerebrovascular autoregulation¹⁴ and probably explains the association between glaucoma and disorders such as vasospasm, endothelial dysfunction, and migraine.^{10,14} Retinal circulation mirrors cerebral circulation,¹⁵ and they share similar anatomic, physiologic, and embryologic characteristics.¹⁶ Abnormalities of the retinal arterioles are a useful indicator of systemic and neurodegenerative diseases such as diabetes, hypertension, multiple sclerosis, Alzheimer disease.¹⁷ Thus, blood flow in the retina is autoregulated in the same way as cerebral blood flow—that is, constant blood flow in the eye is maintained in the retina despite changes in the perfusion pressure,¹³ but only within certain limits. Moreover, the diameter of the blood vessels in the retina depends on the activity of the neurons in the retina. This process is known as neurovascular interaction.

When the ocular perfusion pressure decreases below a patient-specific lower threshold, the autoregulation of the retina blood flow is impaired. Hypothetically, it may lead to the development of glaucoma. As for the brain, the cerebral vascular system must respond

to changes in arterial blood pressure (ABP) or cerebral perfusion pressure (CPP) to maintain stable cerebral blood flow. The mechanism of stabilizing cerebral CPP despite fluctuations in cerebral blood flow is known as cerebrovascular autoregulation. Thus, the blood autoregulation of the central nervous system and that of the eyes is similar, which has inspired a hypothesis that the impairment of eye blood flow in the case of glaucoma is associated with cerebrovascular autoregulation impairment.

Conventional methods for cerebrovascular autoregulation measurement have several limitations (e.g., invasive methods such as surgical access, catheterization, arterial puncture). Several noninvasive methods for cerebrovascular autoregulation monitoring were suggested to overcome these limitations. Transcranial Doppler (TCD) technologies are used to monitor blood flow measurement from the local artery. The mean flow index can provide different information about cerebrovascular autoregulation in patients with strokes, cerebrovascular disease, or traumatic brain injury, depending on the hemisphere.¹⁸ Approximately 10% to 20% of the population are missing the temporal window. Therefore, TCD measurements are impossible for cerebrovascular autoregulation monitoring. In the case of near-infrared spectroscopy (NIRS)-based technologies, regional cerebral oxygen saturation from the external cortex region is used for cerebrovascular autoregulation monitoring.¹⁸ Thus, the main advantage of the volumetric reactivity index (VRx) is the ability to assess cerebrovascular autoregulation more globally, because intracranial blood volume (IBV) changes are measured in both hemispheres, averaging them over the entire acoustic path.¹⁸

The present prospective study applied noninvasive ultrasound techniques to explore the cerebrovascular autoregulation (CA) dynamics in patients with glaucoma (NTG and HTG) and healthy subjects for the first time.

Methods

This prospective clinical study was conducted at the eye clinic of the Lithuanian University of Health Sciences. The study was approved by Kaunas Regional Biomedical Research Ethics Committee (No. BE-2-41, date: September 3, 2013), and according to the Declaration of Helsinki, written informed consent was obtained from all participants.

Patients with glaucoma (HTG and NTG) and healthy subjects were enrolled in the study. The inclusion criteria were as follows: an ophthalmologist-

confirmed clinical diagnosis of glaucoma, the presence of changes in the optic nerve head, and visual field loss consistent with glaucoma. The exclusion criteria were pregnant patients or nursing mothers, patients with uncontrolled systemic diseases, and those with a history of allergy to local anesthetics, orbital/ocular trauma, or other diseases that could bias the study results. Healthy subjects included age-matched volunteers with no history of glaucoma or other diseases that could bias the results.

Thickness of the retinal nerve fiber layer (RNFL) was analyzed using confocal scanning laser ophthalmoscopy (Heidelberg retinal tomography, HRT3, software version 3.1; Heidelberg Engineering, Heidelberg, Germany). Standard automated perimetry was conducted using the Humphrey 24-2 Swedish interactive thresholding algorithm perimeter (Humphrey Standard Perimetry; Carl Zeiss Meditec, 07745 Jena, Germany). Visual field testing was considered unreliable if the fixation losses exceeded 20% and if the false-negative or false-positive errors exceeded 33%. Mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) were assessed. Color Doppler imaging (Accuvix, Seoul, Korea) was used for retrobulbar blood flow measurements in the ophthalmic, central retinal, and short posterior ciliary arteries. In each vessel, peak systolic velocity (PSV) and end-diastolic velocity (EDV) were assessed, and resistance index (RI) was calculated (Porcelot's formula: $RI = (PSV - EDV)/PSV$).

The status of cerebrovascular autoregulation was monitored in participants using the innovative noninvasive ultrasonic technique (Vittamed 505 monitor; Boston Neurosciences, Lexington, MA, USA) based on the ultrasonic time-of-flight (TOF) measurement principle, capable of sensing intracranial density changes within the acoustic path, due to IBV fluctuation used as a surrogate of intracranial pressure (or cerebral blood flow) slow changes for cerebrovascular autoregulation assessment.^{19–22} A head frame with a pair of ultrasonic transducers (2 MHz), positioned on opposite sides of the head on temporal bones, was used to transmit and receive an ultrasound pulse that crossed the brain parenchyma and cerebral ventricles (Fig. A1). Fluctuation of TOF is inversely proportional to changes in IBV because the ultrasound speed in the blood is greater than in other intracranial components (parenchyma and cerebrospinal fluid). Thus, an increase in blood volume within the acoustic path leads to an increase in the average relative ultrasound speed and decrease in TOF changes, $\Delta IBV(t) \sim 1/TOF(t) \sim -\Delta TOF(t)$. Assuming that slow IBV changes are correlated to slow intracranial pressure changes (or slow cerebral blood flow changes), we use reverse $\Delta TOF(t)$ data for the VRx calculation:

$$VRx = r (ABP_{sw}(t); IBV_{sw}) = r (ABP_{sw}(t); -\Delta TOF(t)),^{18,23,24}$$

where $ABP_{sw}(t)$ are arterial blood pressure slow waves, and $IBV_{sw}(t)$ are intracranial blood volume slow waves.

$\Delta TOF(t)$ – slow changes of time-of-flight that inversely reflects slow IBV changes; slow waves with period of 0.5 to 2.0 minutes reflect the vasogenic activity of cerebrovascular autoregulation. ICM + software (Cambridge, UK) was used for monitoring data collection and real-time VRx calculation. The ABP monitor (Finapres Nova, Enschede, Netherlands) was employed for this study (Fig. A1). The sampling frequency of TOF data collection was 50 Hz. Two-minute moving time windows of slow IBV(t) and ABP(t) slow waves were used for temporary VRx(t) calculation.^{18,23} A band-pass filter as used to extract waves from IBV and ABP data.

The CA monitoring session lasted up to 15 minutes for each subject. All subjects were asked to perform the Valsalva maneuver (up to 15–20 seconds) once per minute to generate repetitive slow waves and physiologic reactions needed for CA assessment.²⁵ Negative values ($VRx(t) < 0$) correspond to intact CA status, whereas positive values ($VRx(t) > 0$) indicate CA impairment.^{18,23}

For each episode of CA impairment, we estimated the duration of the single longest CA impairment event (LCAI) and the LCAI dose. The LCAI duration was calculated using thresholds of $VRx > 0$, which represents the mathematical threshold for CA impairment, in which $VRx > 0.4$, associated with patient outcome (similar thresholds of 0.4–0.5 are also used for other noninvasive CA indexes, such as the mean flow index [transcranial Doppler-based CA measurements]²⁶ and cerebral oximetry index [NIRS-based CA indexes]).²⁷ The LCAI dose was calculated as the area under the curve of $VRx > 0$. The average VRx, duration of a single LCAI event, and LCAI dose were chosen to evaluate and compare the CA impairment in patients with glaucoma and healthy subjects.

Statistical data analysis was conducted using IBM SPSS (version 23.0; IBM Corporation, Armonk, NY, USA). All variables were defined and summarized using descriptive statistics, presented as the mean values and standard deviations (SDs). The Shapiro–Wilk normality test was used to assess normal distribution. The Mann–Whitney *U* test was used to calculate differences between continuous variables and differences between groups for two independent samples. The Kruskal–Wallis test was used to calculate differences between continuous variables and differences between groups for more than two independent samples.

Results

In this prospective clinical study, the 28 participants were divided into three groups: 10 patients with NTG, 8 patients with HTG, and 10 healthy subjects. [Table 1](#) presents the composition of the study groups. In healthy subjects, the means of RNFL thickness in

superior, nasal, inferior, and temporal quadrants were measured as 124.1 ± 13.6 , 79.8 ± 12.2 , 142.4 ± 13.4 , and $76.6 \pm 9.0 \mu\text{m}$, respectively. In the case of NTG, the means of RNFL thickness in superior, nasal, inferior, and temporal quadrants were 106.9 ± 19.3 , 76.9 ± 13.4 , 111.0 ± 35.4 , and $67.9 \pm 12.5 \mu\text{m}$, respectively. However, the means of RNFL thickness in superior, nasal, inferior, and temporal quadrants of

Table 1. Basic Parameters of the Study Group

Characteristic	HS	NTG	HTG	χ^2	df	P Value
Number of subjects	10	10	8	—	—	—
Age, mean \pm SD, y	71.1 \pm 5.1 ^b	67.5 \pm 2.3 ^c	73.2 \pm 2.7 ^{b,c}	12.899	2	0.020
Gender (male), %	20	10	12.5	—	—	—
Body mass index, mean \pm SD	27.97 \pm 5.01	28.49 \pm 5.37	26.93 \pm 3.18	0.140	2	0.932
Family members with glaucoma, %	0	40	0	—	—	—
Glaucoma surgery	No	No	No	—	—	—
Illness period, mean \pm SD, y	—	4.3 \pm 4.98	4.97 \pm 5.03	1.361	1	0.243
Glaucoma medications, n (%)						
β -Blockers	0 (0)	2 (20)	2 (25)	—	—	—
Pg analogues	0 (0)	7 (70)	5 (62.5)	—	—	—
CAIs, N (%)	0 (0)	4 (40)	3 (37.5)	—	—	—
α 2-Agonists	0 (0)	0 (0)	4 (50)	—	—	—
Systemic medications, n (%)						
Diuretics	0 (0)	0 (0)	2 (25)	—	—	—
β -Blockers	2 (20)	6 (60)	5 (62.5)	—	—	—
ACE inhibitors	1 (10)	1 (10)	0 (0)	—	—	—
ARBs	1 (10)	1 (10)	0 (0)	—	—	—
Others	8 (80)	9 (90)	4 (50)	—	—	—
Mean ABP, mean \pm SD, mm Hg	98.3 \pm 5.5	104.7 \pm 9.3	97.4 \pm 13.7	3.110	2	0.211
IOP, mean \pm SD, mm Hg	14.5 \pm 2.0 ^b	14.2 \pm 1.7 ^c	18.9 \pm 4.8 ^{b,c}	8.034	2	0.018
OPP, mean \pm SD, mm Hg	55.9 \pm 4.3 ^a	60 \pm 4.9 ^a	52.4 \pm 9.9	5.561	2	0.059
RNFL, mean \pm SD, μm	106.7 \pm 8.0 ^{a,b}	90.8 \pm 16.7 ^a	77.0 \pm 25.1 ^b	9.837	2	0.007
Superior RNFL, mean \pm SD, μm	124.1 \pm 13.6 ^b	106.9 \pm 19.3	85.1 \pm 37.5 ^b	6.527	2	0.038
Nasal RNFL, mean \pm SD, μm	79.8 \pm 12.2	76.9 \pm 13.4	63.8 \pm 27.4	2.286	2	0.319
Inferior RNFL, mean \pm SD, μm	142.4 \pm 13.4 ^{a,b}	111.0 \pm 35.4 ^a	96.1 \pm 28.4 ^b	12.406	2	0.002
Temporal RNFL, mean \pm SD, μm	76.6 \pm 9.0	67.9 \pm 12.5	59.5 \pm 21.3	3.415	2	0.181
Visual field parameters						
MD, mean \pm SD, dB	-0.89 \pm 0.62 ^{a,b}	-4.37 \pm 2.96 ^a	-6.76 \pm 6.67 ^b	4.921	2	0.007
PSD, mean \pm SD, dB	1.65 \pm 0.35 ^a	4.79 \pm 2.67 ^a	5.60 \pm 4.88	6.793	2	0.014
VFI, mean \pm SD, %	98.80 \pm 0.63 ^{a,b}	90.20 \pm 7.89 ^a	84.88 \pm 17.21 ^b	5.934	2	0.005

P value is based on nonparametric Kruskal–Wallis test for more than two independent samples. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAI, carbonic anhydrase inhibitors; HS, healthy subjects; OPP, ocular perfusion pressure; Pg, prostaglandin; —, XXX.

^aCases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and NTG.

^bCases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and HTG.

^cCases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between NTG and HTG.

Bold values indicate that $p < 0.05$.

Table 2. Flow Velocities and Resistance Index in the Ophthalmic, Central Retinal, and Short Posterior Ciliary Arteries at Baseline

Characteristic	HS (n = 10), Mean ± SD	NTG (n = 10), Mean ± SD	HTG (n = 8), Mean ± SD	χ^2	df	P Value
Ophthalmic artery						
Peak systolic velocity, cm/s	34.38 ± 8.51	31.80 ± 8.34	35.53 ± 7.49	0.498	2	0.780
End-diastolic velocity, cm/s	6.83 ± 1.81	8.01 ± 2.43	9.88 ± 4.73	2.860	2	0.239
Resistance index	0.79 ± 0.05	0.75 ± 0.04	0.73 ± 0.06	4.305	2	0.116
Central retinal artery						
Peak systolic velocity, cm/s	9.31 ± 2.28	10.15 ± 2.05	9.89 ± 2.01	0.836	2	0.658
End-diastolic velocity, cm/s	3.33 ± 0.52	3.55 ± 0.84	3.48 ± 0.44	0.594	2	0.743
Resistance index	0.62 ± 0.06	0.64 ± 0.06	0.63 ± 0.07	0.188	2	0.910
Short posterior ciliary arteries						
Peak systolic velocity, cm/s	8.06 ± 1.24	8.84 ± 1.63	8.24 ± 1.92	1.125	2	0.570
End-diastolic velocity, cm/s	4.19 ± 0.92	4.05 ± 0.49	3.87 ± 0.58	0.547	2	0.761
Resistance index	0.47 ± 0.04	0.53 ± 0.07	0.51 ± 0.09	2.430	2	0.297

P value is based on nonparametric Kruskal–Wallis test for more than two independent samples.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and NTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and HTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between NTG and HTG.

Table 3. Cerebrovascular Autoregulation-Related Parameters

Characteristic	HS (n = 10), Mean ± SD	NTG (n = 10), Mean ± SD	HTG (n = 8), Mean ± SD	χ^2	df	P Value
VRx, mean ± SD	-0.18 ± 0.22 ^a	0.06 ± 0.17 ^a	-0.07 ± 0.25	5.362	2	0.068
LCAI duration, mean ± SD, VRx > 0, s	127 ± 66 ^a	281 ± 151 ^a	231 ± 218	7.858	2	0.020
LCAI duration, mean ± SD, VRx > 0.4, s	13 ± 38 ^a	73 ± 59 ^a	42 ± 65	7.156	2	0.028
LCAI dose, mean ± SD, s	31 ± 29 ^a	107 ± 77 ^a	75 ± 85	8.794	2	0.012

P value is based on nonparametric Kruskal–Wallis test for more than two independent samples.

^aCases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and NTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between HS and HTG.

Cases of statistically significant ($P < 0.05$) differences between two independent samples based on Mann–Whitney test between NTG and HTG.

Bold values indicate that $p < 0.05$.

HTG were 85.1 ± 37.5 , 63.8 ± 27.4 , 96.1 ± 28.4 , and $59.5 \pm 21.3 \mu\text{m}$, respectively. Statistically significant differences were detected between the three groups, as shown in Table 1. Patients with glaucoma had significantly worse visual field measures (VFI, MD, PSD) compared to healthy subjects.

Table 2 shows the flow velocities and RI in the ophthalmic, central retinal, and short posterior ciliary arteries at baseline. No significant difference was detected in blood flow velocities. The RI in all three vessels did not differ in the three study populations.

Table 3 shows the CA monitoring results. From the Shapiro–Wilk normality test, the CA monitoring data failed to show a normal distribution; therefore, a comparison was made by the Mann–Whitney U test. The average VRx was -0.18 ± 0.22 for healthy subjects, 0.06 ± 0.17 for patients with NTG, and -0.07 ± 0.25 for patients with HTG. The VRx value for healthy subjects was significantly lower than that of patients with NTG ($P < 0.05$). No significant differences were noted between the healthy subjects and HTG groups and between the NTG and HTG groups ($P = 0.36$ and

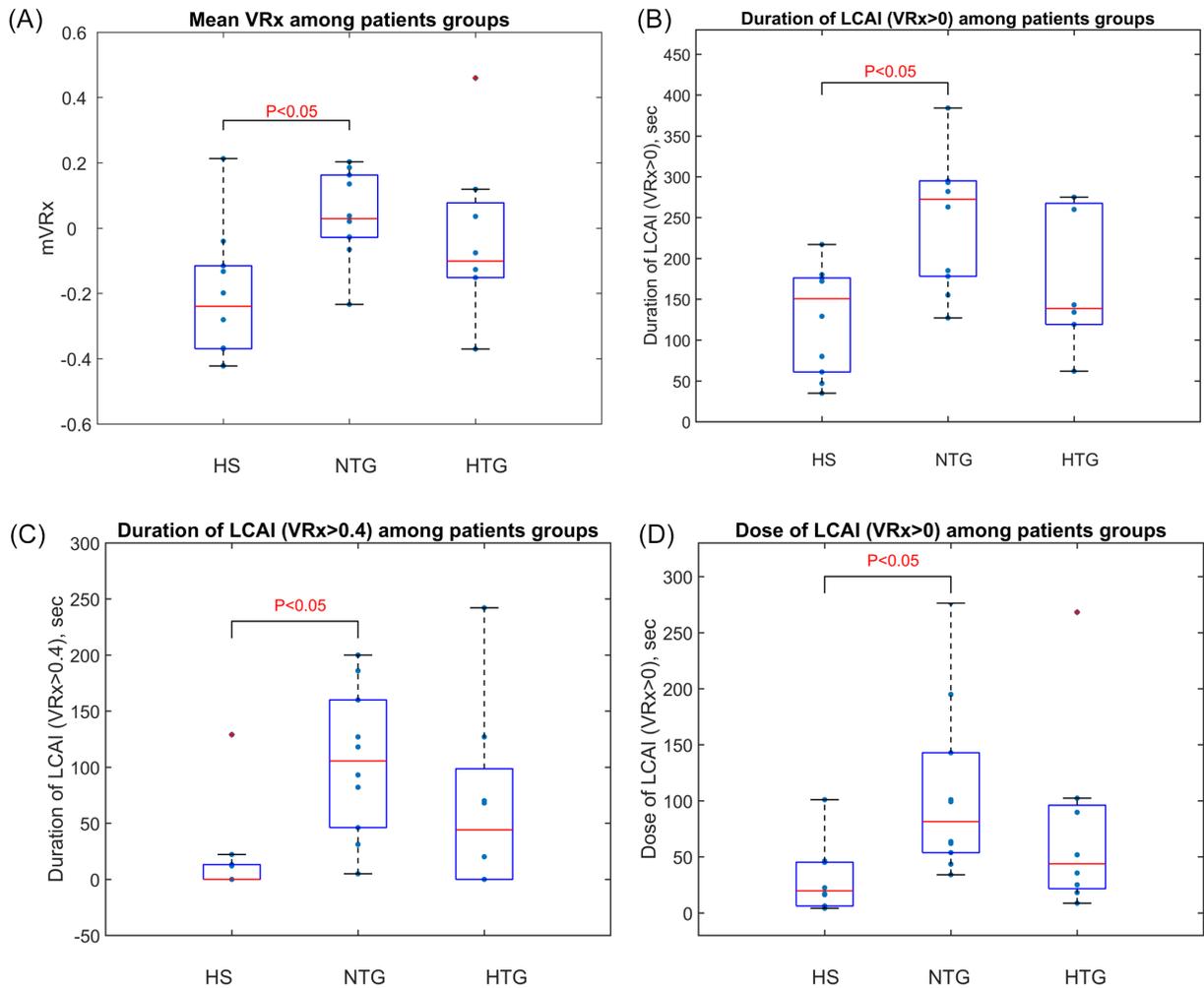


Figure 1. (A) Distribution of VRx among the study groups. (B) Longest cerebral autoregulation impairment event duration (VRx > 0) for different study groups. (C) Longest cerebral autoregulation impairment event duration (VRx > 0.4) for different study groups. (D) Longest cerebral autoregulation impairment event dose for different study groups. The longest cerebral autoregulation impairment event dose was calculated as the area under VRx > 0 curve. HS, healthy subjects.

$P = 0.24$, respectively). The VRx distribution among study groups is presented in Figure 1A.

The LCAI duration (VRx > 0) was 127 ± 66 seconds for healthy subjects, 281 ± 151 seconds for patients with NTG, and 231 ± 218 seconds for patients with HTG. The LCAI duration for healthy subjects was significantly lower than that of patients with NTG ($P < 0.05$). However, no significant differences were noted between healthy subjects and patients with HTG and between patients with NTG and HTG ($P = 0.35$ and $P = 0.10$, respectively). The results of the LCAI duration for the study groups are shown in Figure 1B.

The LCAI duration (VRx > 0.4) was 13 ± 38 seconds in healthy subjects, 73 ± 59 seconds in patients with NTG, and 42 ± 65 seconds in patients with HTG. The LCAI duration of healthy subjects was

significantly lower than in patients with NTG ($P < 0.05$). However, no significant differences were noted between healthy subjects and patients with HTG and between patients with NTG and HTG ($P = 0.20$ and $P = 0.15$, respectively). The results of the study group's LCAI duration are shown in Figure 1C.

The LCAI dose (VRx > 0) was 31 ± 29 seconds in healthy subjects, 107 ± 77 seconds in patients with NTG and 75 ± 85 seconds in patients with HTG. The LCAI dose of healthy subjects was significantly lower than that of the patients with NTG ($P < 0.05$). However, no significant differences were noted between healthy subjects and patients with HTG and between patients with NTG and HTG ($P = 0.12$ and $p = 0.17$, respectively). The results of the LCAI dose for different study groups are presented in Figure 1D.

Discussion

In this prospective clinical study, compromised cerebral autoregulation was observed in patients with NTG through CA impairment parameters based on VRx and the duration and doses of LCAI. No statistically significant difference was noted between patients with HTG and healthy subjects. The findings support our hypothesis regarding the association between CA impairments and NTG development, showing that NTG can disturb cerebral blood flow rather than eye pathology.

Other studies also present the hypothesis regarding the role of CA in NTG or glaucoma formation. Tutaj et al.¹⁴ suggested that the compromised CA in patients with glaucoma can be associated with vascular dysregulation. Impaired vascular autoregulation that causes nonconstant blood flow to the retina and optic nerve may contribute to changes in the optic nerve head, thereby provoking glaucoma.

Cerebrovascular disease plays a critical role in the pathogenesis of glaucoma²⁸ and is more frequent in patients with NTG than in patients with HTG or healthy subjects.²⁹ Thus, our prospective clinical research provides evidence of cerebrovascular dysfunction in patients with NTG. Recent studies have shown reduced cerebrovascular blood flow velocities^{30,31} and increased risk of Alzheimer disease or other dementia in patients with NTG.³² However, few studies revealed changes in a hemodynamic parameter of the middle cerebral artery in patients with glaucoma.^{30,33,34}

Thus, glaucoma progression is associated with decreased cerebral blood flow.³⁵ Moreover, vascular insufficiency through unstable ocular blood flow leads to retinal ganglion cell loss^{36,37} and visual field deficits. Therefore, glaucoma plays an important role in the pathogenesis of glaucomatous optic neuropathy.³⁸ Treatment based on the increasing systematic blood flow can improve the visual field in some patients with NTG.^{39,40} The endothelium is the primary regulator of vascular homeostasis,⁴¹ and it plays a vital role in controlling blood flow.^{40,42} Although several studies have shown endothelial dysfunction in patients with NTG,^{42–44} direct evidence of local ocular endothelial dysfunction is difficult to establish. Therefore, the link between endothelial dysfunction and progression in patients with NTG is unclear.

Our findings and evidence from other studies discussed above independently confirm the NTG association between cerebral blood flow pathology and disturbed CA. Therefore, a CA assessment test (Valsalva maneuver,¹⁸ cold pressor,⁴⁵ squat-stand,⁴⁶ etc.) using noninvasive technologies (VRx, TCD, or

NIRS) is recommended for personalized identification of glaucoma-related factors and for choosing appropriate treatments for patients with NTG and HTG.

For CA assessment, we have chosen a noninvasive ultrasonic TOF technique capable of deriving CA-related VRx indexes from IBV fluctuation averaged over the ultrasound wave propagation path from the left to right sides of the temporal bones crossing both hemispheres. The ability to provide a more global CA estimation over the entire cranium is the main advantage of the VRx-based CA assessment technique over other noninvasive CA assessment techniques (TCD or NIRS based). The TCD-based technique is based on blood flow measurement in regional cerebral arteries, and the NIRS-based technique measures intracranial blood fluctuations in the cortex only, which is limited to a 2- to 3-cm depth. Moreover, the application of the TCD-based technique is limited due to temporal window failure in 8% to 20% of the subjects.⁴⁷ Meanwhile, the TOF technique used in this study can measure IBV fluctuation for all tested subjects. A study that tested this novel noninvasive TOF technique for patients with TBI showed a significant coincidence between noninvasive (VRx) CA and invasive (pressure reactivity index) CA, estimating the significant associations between VRx indexes and outcome of patients with TBI.¹⁸ An additional clinical study of this noninvasive CA technique on cardiac surgery patients with cardiopulmonary bypass showed that duration of CA impairment events more than 5 minutes during surgery is associated with postoperative cognitive deterioration.¹⁵

Our previous studies also showed that CA impairment events and their duration can be detected using the VRx index at different thresholds: $VRx > 0$ and $VRx > 0.4$, a theoretical threshold value separating intact CA ($VRx < 0$) and impaired CA ($VRx > 0$). In this study, we obtained the highest statistical significance between healthy subjects and NTG groups when measuring the LCAI duration with a threshold of $VRx > 0.4$ (Table 3, Fig. 1C). Similar thresholds (0.4–0.5) have also been used for other noninvasive CA indexes (pressure reactivity index, mean flow index, and cerebral oximetry index) to detect CA impairment^{26,27,48} in the noisy data and cases with low slow-wave amplitude. The limited number of patients in the groups was the main limitation of this pilot study. Larger numbers of subjects are needed to obtain statistically significant results and test the hypothesis regarding the relationship between glaucoma and CA impairments. Another limitation is the absence of a gold-standard index of CA. The invasive pressure reactivity index requires invasive sensors as it only provides a rough estimate of CA status, and it is used

only for patients with TBI. Our previous prospective clinical studies showed that the VRx index could be used for CA assessment in patients with TBI¹⁸ and patients undergoing cardiac surgery with cardiopulmonary bypass.²³

Conclusion

In this pilot study, we demonstrated that NTG is associated with disturbed cerebral blood flow, which can be diagnosed by performing noninvasive CA assessments based on VRx monitoring. Further clinical studies are needed to prove this hypothesis.

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References

- Chen Y, Hughes G, Chen X, et al. Genetic variants associated with different risks for high tension glaucoma and normal tension glaucoma in a Chinese population. *Invest Ophthalmol Vis Sci*. 2015;56(4):2595–2600.
- He Z, Vingrys AJ, Armitage JA, Bui BV. The role of blood pressure in glaucoma. *Clin Exp Optom*. 2011;94(2):133–149.
- Omoti A, Enock M, Okeigbemen V, Akpe B, Fuh U. Vascular risk factors for open angle glaucoma in African eyes. *Middle East Afr J Ophthalmol*. 2009;16(3):146–150.
- Shoeb Ahmad S, Abdul Ghani S, Hemalata Rajagopal T. Current concepts in the biochemical mechanisms of glaucomatous neurodegeneration. *J Curr glaucoma Pract*. 2013;7(2):49–53.
- Yan DB, Coloma FM, Metheetrairut A, Trope GE, Heathcote JG, Ethier CR. Deformation of the lamina cribrosa by elevated intraocular pressure. *Br J Ophthalmol*. 1994;78(8):643–648.
- Flammer J, Orgül S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res*. 2002;21(4):359–393.
- Flammer J. The vascular concept of glaucoma. *Surv Ophthalmol*. 1994;38:S3–S6.
- Plange N, Remky A, Arend O. Colour Doppler imaging and fluorescein filling defects of the optic disc in normal tension glaucoma. *Br J Ophthalmol*. 2003;87(6):731–736.
- Flammer J, Orgül S. Optic nerve blood-flow abnormalities in glaucoma. *Prog Retin Eye Res*. 1998;17(2):267–289.
- Moore D, Harris A, Wudunn D, Kheradiya N, Siesky B. Dysfunctional regulation of ocular blood flow: a risk factor for glaucoma? *Clin Ophthalmol*. 2008;2(4):849–861.
- Schmidl D, Garhofer G, Schmetterer L. The complex interaction between ocular perfusion pressure and ocular blood flow—relevance for glaucoma. *Exp Eye Res*. 2011;93(2):141–155.
- Fan N, Wang P, Tang L, Liu X. Ocular blood flow and normal tension glaucoma. *Biomed Res Int*. 2015;12:308505.
- Luo X, Shen YM, Jiang MN, Lou XF, Shen Y. Ocular blood flow autoregulation mechanisms and methods. *J Ophthalmol*. 2015;2015:864871.
- Tutaj M, Brown CM, Brys M, et al. Dynamic cerebral autoregulation is impaired in glaucoma. *J Neurol Sci*. 2004;220(1–2):49–54.
- Harris A, Ciulla TA, Chung HS, Martin B. Regulation of retinal and optic nerve blood flow. *Arch Ophthalmol*. 1998;116(11):1491–1495.
- Wong TY, Mitchell P. The eye in hypertension. *Lancet*. 2007;369(9559):425–435, doi:10.1016/S0140-6736(07)60198-6.
- Hui F, Nguyen CTO, He Z, et al. Retinal and cortical blood flow dynamics following systemic blood-neural barrier disruption. *Front Neurosci*. 2017;11:568.
- Petkus V, Preiksaitis A, Krakauskaitė S, et al. Non-invasive cerebrovascular autoregulation assessment using the volumetric reactivity index: prospective study. *Neurocrit Care*. 2019;30(1):42–50.
- Ragauskas A, Daubaris G, Petkus V, Ragaisis V, Ursino M. Clinical study of continuous non-invasive cerebrovascular autoregulation

- monitoring in neurosurgical ICU. *Acta Neurochir Suppl.* 2005;95:367–370.
20. Petkus V, Preiksaitis A, Krakauskaitė S, et al. Novel method and device for fully non-invasive cerebrovascular autoregulation monitoring. *Elektron Elektrotechnika.* 2014;20(8):24–29.
 21. Petkus V, Ragauskas A, Jurkonis R. Investigation of intracranial media ultrasonic monitoring model. *Ultrasonics.* 2002;40(1–8):829–833.
 22. Petkus V, et al. Novel technology of non-invasive cerebrovascular autoregulation monitoring, *IEEE 27th International Symposium on Computer-Based Medical Systems.* 2014:427–430, doi:10.1109/CBMS.2014.44.
 23. Kumpaitienė B, Svagzdiene M, Sirvinskas E, et al. Cerebrovascular autoregulation impairments during cardiac surgery with cardiopulmonary bypass are related to postoperative cognitive deterioration: prospective observational study. *Minerva Anesthesiol.* 2019;85(6):594–603.
 24. Ragauskas A, Daubaris G, Ragaisis V, Petkus V. Implementation of non-invasive brain physiological monitoring concepts. *Med Eng Phys.* 2003;25(8):667–678.
 25. Castro PM, Santos R, Freitas J, Panerai RB, Azevedo E. Autonomic dysfunction affects dynamic cerebral autoregulation during Valsalva maneuver: comparison between healthy and autonomic dysfunction subjects. *J Appl Physiol.* 2014;117(3):205–213.
 26. Zheng Y, Villamayor AJ, Merritt W, et al. Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation. *Neurocrit Care.* 2012;17(1):77–84.
 27. Joshi B, Ono M, Brown C, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg.* 2012;114(3):503–510.
 28. Kitsos G, Zikou A, Bagli E, Kosta P, Argyropoulou M. Conventional MRI and magnetisation transfer imaging of the brain and optic pathway in primary open-angle glaucoma. *Br J Radiol.* 2009;82(983):896–900.
 29. Lee M-S, Kuo L-L, Tan EC-H, Lee OK. Is normal-tension glaucoma a risk factor for stroke? A 10-year follow-up study. *PLoS One.* 2017;12(6):e0179307.
 30. Harris A, Zarfati D, Zalish M, et al. Reduced cerebrovascular blood flow velocities and vasoreactivity in open-angle glaucoma. *Am J Ophthalmol.* 2003;135(2):144–147.
 31. Sugiyama T, Utsunomiya K, Ota H, Ogura Y, Narabayashi I, Ikeda T. Comparative study of cerebral blood flow in patients with normal-tension glaucoma and control subjects. *Am J Ophthalmol.* 2006;141(2):394–396.
 32. Bayer AU, Ferrari F, Erb C. High occurrence rate of glaucoma among patients with Alzheimer's disease. *Eur Neurol.* 2002;47(3):165–168.
 33. Harris A, Siesky B, Zarfati D, et al. Relationship of cerebral blood flow and central visual function in primary open-angle glaucoma. *J Glaucoma.* 2007;16(1):159–163.
 34. Akarsu C, Bilgili YK, Unal B, Taner P, Ergin A, Kara SA. Cerebral hemodynamics in ocular hypertension. *Graefes Arch Clin Exp Ophthalmol.* 2005;243(4):317–320.
 35. Harris A, Siesky B, Wirostko B. Cerebral blood flow in glaucoma patients. *J Glaucoma.* 2013;22(suppl 5):S46–S48.
 36. Yamazaki Y, Drance SM. The relationship between progression of visual field defects and retrobulbar circulation in patients with glaucoma. *Am J Ophthalmol.* 1997;124(3):287–295.
 37. Killer HE, Pircher A. Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis. *Eye.* 2018;32(5):924–930.
 38. Osborne NN, Melena J, Chidlow G, Wood JPM. A hypothesis to explain ganglion cell death caused by vascular insults at the optic nerve head: possible implication for the treatment of glaucoma. *Br J Ophthalmol.* 2001;85(10):1252LP–1259LP.
 39. Kitazawa Y, Shirai H, Go FJ. The effect of Ca²⁺(+) -antagonist on visual field in low-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol.* 1989;227(5):408–412.
 40. Buckley C, Hadoke PWF, Henry E, O'Brien C. Systemic vascular endothelial cell dysfunction in normal pressure glaucoma. *Br J Ophthalmol.* 2002;86(2):227–232.
 41. Fountoulakis P, Oikonomou E, Lazaros G, Tousoulis D. Endothelial function. In *Coronary Artery Disease: From Biology to Clinical Practice.* Elsevier; 2017:13–30, <https://doi.org/10.1016/B978-0-12-811908-2.00002-7>.
 42. Su W-W, Cheng S-T, Hsu T-S, Ho W-J. Abnormal flow-mediated vasodilation in normal-tension glaucoma using a noninvasive determination for peripheral endothelial dysfunction. *Invest Ophthalmol Vis Sci.* 2006;47(8):3390–3394.
 43. Henry E, Newby DE, Webb DJ, O'Brien C. Peripheral endothelial dysfunction in normal pressure glaucoma. *Invest Ophthalmol Vis Sci.* 1999;40(8):1710–1714.

44. Resch H, Garhofer G, Fuchsjäger-Mayrl G, Hommer A, Schmetterer L. Endothelial dysfunction in glaucoma. *Acta Ophthalmol.* 2009;87(1):4–12.
45. Ikemura T, Someya N, Hayashi N. Autoregulation in the ocular and cerebral arteries during the cold pressor test and handgrip exercise. *Eur J Appl Physiol.* 2012;112(2):641–646.
46. Barnes SC, Ball N, Haunton VJ, Robinson TG, Panerai RB. How many squat-stand manoeuvres to assess dynamic cerebral autoregulation? *Eur J Appl Physiol.* 2018;118(11):2377–2384.
47. Lee C-H, Jeon S-H, Wang S-J, Shin B-S, Kang HG. Factors associated with temporal window failure in transcranial Doppler sonography. *Neurol Sci.* 2020;41(11):3293–3299.
48. Lee JK, Kibler KK, Benni PB, et al. Cerebrovascular reactivity measured by near-infrared spectroscopy. *Stroke.* 2009;40(5):1820–1826.

Appendix

Figure A1.



Figure A1. The CA monitoring setup includes the noninvasive ultrasonic TOF monitoring device with the head frame, noninvasive blood pressure monitoring device, and a personal computer with “ICP+” software for real-time calculation of CA index (VRx). A head frame bearing a pair of ultrasonic transducers (2 MHz) on either side of the patient’s head was positioned to transmit and receive the ultrasound wave.