Assessment of Cerebral Vasomotor Reactivity in Patients With Primary Open-angle Glaucoma and Ocular Hypertension Using the Breath-Holding Index

Gurcan D. Arslan, MD, Ali Olgun, MD,† Delil Ozcan, MD,‡ Elif Gökcal, MD,§ Dilek Guven, MD,‡ and Talip Asil, MD§*

Précis: Patients with ocular hypertension (OHT) do not show impaired cerebral vasodilation responses to hypercapnia but patients with primary open-angle glaucoma (POAG) do. Impaired vasoreactivity in patients with POAG may have neuronal or vascular origins and increase stroke risk.

Purpose: To investigate changes in cerebral blood flow and cerebral vasomotor reactivity using the breath-holding index in patients with POAG and OHT, to examine whether these parameters contribute to the risk of ischemic stroke.

Methods: Thirty patients with POAG, 30 patients with OHT, and 30 age- and sex-matched healthy control subjects were included in this university hospital-based, cross-sectional, and observational study. Eyes with a greater degree of visual field loss and/or more severe optic disc damage were selected for the study in patients with POAG, whereas in patients with OHT and controls, the study eye was chosen randomly. The mean blood flow velocity and breath-holding index were measured in the middle cerebral artery ipsilaterally in patient and control groups, by using transcranial Doppler ultrasonography.

Results: The mean blood flow velocity and breath-holding indexes were significantly lower in patients with POAG than in the control group (all $P < 0.05$). In the OHT group, the mean blood flow velocity and breath-holding indexes were not different from those in the control group.

Conclusions: Patients with POAG have impaired vasodilation response to hypercapnia. Presumably, the neuronal changes and deterioration of the endothelium-mediated vasodilatation in patients with glaucoma may disrupt the regulation of arteries and potentially present functional insufficiency on vasoreactivity. Moreover, impaired cerebral vascular regulation may contribute to the increased risk of stroke in patients with POAG.

Key Words: primary open-angle glaucoma, ocular hypertension, cerebral blood flow, breath-holding index

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Glaucoma is one of the leading causes of irreversible blindness globally.[1] It is a progressive eye disease characterized by optic neuropathy and visual field loss. The most common form is primary open-angle glaucoma (POAG).[2] It is not known exactly how optic nerve damage occurs in POAG. As increased intraocular pressure (IOP) is one of the most important risk factors,[3] suggesting a mechanical etiology, systemic risk factors, such as diabetes,[4] hypertension,[5,6] and stroke,[7] have been shown to play a role, and suggest an etiology involving impaired vascular perfusion. In addition, although systemic comorbidities, particularly hypertension and diabetes, are seen as important risk factors for stroke in patients with POAG, the pathophysiological connection between POAG and stroke has not been clarified to date.[8]

Although the IOP is increased in ocular hypertension (OHT), optic nerve damage and visual field loss are not observed. However, OHT is a well-known risk factor for the development of POAG.[9] Moreover, topical ocular hypotensive medication was found to be effective for delaying or preventing the onset of POAG in patients with OHT.[10] In the OHT treatment study, the high proportion of participants (42%) who reported a family history of glaucoma suggested that glaucoma is not always distinguishable from OHT.[11]

There is increasing evidence that low ocular blood flow plays an important role in the pathogenesis of glaucomatous optic neuropathy.[12] It has been reported that patients with mild to moderate POAG have decreased cerebral blood flow (CBF) in early visual cortical areas and that CBF reduction in these cortical areas is associated with optic disc damage.[13] In addition, in a study examining retrobulbar blood flow in patients with glaucoma, altered autoregulation was observed and it was suggested that this may contribute to disease progression.[14]

CBF rises if there is an increase in arterial carbon dioxide (CO_2) concentration and a decrease in arterial pH.[15] These effects are mediated by changes in diameters of cerebral arterioles; thus, this phenomenon is termed as cerebral vasomotor reactivity (CVMR).[16] Impaired CVMR is presumed to be associated with an increased risk of ischemic events or stroke.[17,18] To evaluate CVMR, transcranial Doppler (TCD) ultrasonography has been used in conjunction with transient hypercapnial vasodilator stimulants, such as acetazolamide, CO_2 inhalation, or the breath-hold test.[19–22] The breath-holding index (BHI) is used to evaluate the alteration in CBF velocity in response to a breath-hold challenge, which induces hypercapnia.[23] It has been shown that cerebrovascular autoregulation is compromised in patients with POAG.[24] However, no study has evaluated whether there are any potential associations between POAG and CVMR with hypercapnia.

We assumed that impaired CVMR may be responsible for the changes in CBF and may contribute to an increased risk of ischemic stroke in patients with POAG. In addition,

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From the *Department of Ophthalmology, Tatvan State Hospital, Bitlis; †Dunya Goz Altunizade; ‡Department of Ophthalmology, University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital; and §Department of Neurology, Bezmialem Vakif University School of Medicine, Istanbul, Turkey.
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Reprints: Gurcan D. Arslan, MD, Department of Ophthalmology, Tatvan State Hospital, 45 Hal Street, Tatvan, Bitlis 13200, Turkey (e-mail: mr.dogukan2@gmail.com).

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patients with OHT form a heterogenous group that includes some healthy subjects, and some possible patients with preglaucoma. Therefore, this study evaluated CVMR in patients with OHT and POAG by assessing the mean blood flow velocities (BFVs) and BHI using TCD ultrasonography to investigate the relationship between these 2 groups of patients and CVMR with hypercapnia.

METHODS

Participants and Data Collection

This study was approved by Şişli Hamidiye Etfal Training and Research Hospital's ethics committee and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each study participant after an explanation of the nature and possible consequences of the study.

Thirty patients with POAG, 30 patients with OHT, and 30 age- and sex-matched healthy controls were included in this observational, cross-sectional study. Medical history was taken and complete ophthalmic examinations were performed for all participants at the ophthalmology clinic of the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital.

Inclusion criteria for patients with POAG were bilateral glaucomatous-type optic disc cupping, with localized visual field defects, and the presence of nerve fiber layer defects in each eye. In addition, an open anterior chamber angle was visualized on gonioscopy, and repeated pretreatment IOP readings were over 21 mm Hg. Patients were excluded if they had cup-to-disc ratios of ≥ 0.9 or a mean deviation ≥ 8 dB of visual fields. Patients with pseudoexfoliation syndrome, pigmentary glaucoma, and patients with a history of intraocular surgery were not included.

Patients with OHT were included if they had normal visual fields on the 24-2 Full Threshold Test (Humphrey Instruments, San Leandro, CA), a clinically normal optic disc, and an IOP of >21 mm Hg (noncontact tonometry, NT-530P, Nidek Co. Ltd, Gamagori, Japan), on 3 separate measurements. The IOP measurements were also repeated with Goldmann applanation tonometry. A normal optic nerve head was defined as a cup-to-disc ratio <0.4, vertical asymmetry <0.2, and an intact neuroretinal rim without peripapillary hemorrhages. Individuals in the control group had no history of ocular or systemic pathology and had normal outcomes on eye examination.

All individuals in the study had a best-corrected visual acuity of 0.30 logarithm of the minimum angle of resolution (logMAR; equivalent to 20/40 on a Snellen chart) or better, and a refractive error ranging between +3.00 to −6.00 diopters. All patients who were on treatment with topical hypotensive medication discontinued the medication use 3 days before the examination. We discontinued topical medication because of the possibility of systemic absorbance of topical medication agents and their prolonged systemic effects, although plasma concentrations of topical medication agents are low and usually decrease within several hours after the application.[25,26] Patients who were not eligible to discontinue the treatment were not included in the study. The topical medication in patients included prostaglandin analogues, carbonic anhydrase inhibitors, and beta-blockers, as sole therapy or in combination. Further exclusion criteria included patients with diabetes, central nervous system diseases, cardiovascular diseases, or coexisting vitreoretinal diseases; patients on systemic antihypertensive medication therapy; and patients with nonglaucomatous optic nerve damage.

Study Design

In patients with POAG, the eye with the greater degree of visual field loss and/or more severe optic disc damage was selected for the study. The study eye of the patients with OHT was randomly selected for analysis if both eyes were eligible. Moreover, in the control group, the study eye was also selected randomly. The mean BFV and BHI of participants were measured at the ipsilateral middle cerebral artery (MCA) with TCD ultrasonography (SONORA, CareFusion, San Diego, CA). Measurements included brachial arterial pressure, heart rate, peripapillary retinal nerve fiber layer (RNFL), and macular ganglion cell complex (GCC) thickness, measured using spectral-domain optical coherence tomography (SD-OCT; Topcon 3D OCT-2000, Topcon Inc., Japan).

SD-OCT Measurements

Macular GCC and peripapillary RNFL thickness were measured using SD-OCT. We devised 3-dimensional scans of the macular region, termed the GCC scan, which samples the macula over a 7×7 mm² vertical scan area in a 0.6-seconds limited scan time. The scan pattern consists of 128×512 pixels taken in a 7×7 mm² area with an interval of 0.05 mm. GCC parameters were analyzed in terms of the average thickness, and superior and inferior region thicknesses. In the measurement of the peripapillary RNFL thickness, the reference plane height of disc topography was 120 μm. SD-OCT automatically delineated the optic disc margin and calculated the center of the optic disc. The peripapillary RNFL thickness was calculated as the distance between the anterior and posterior RNFL borders in a ring with a 3.45-mm radius, centered on the optic disc. The peripapillary RNFL thickness measurement targeted the area that is between the ring with a 3.45-mm radius and the optic disc margin. The average peripapillary RNFL thickness corresponding to the superior and inferior hemifields was measured. Images were excluded if the image quality was <60. The SD-OCT scans were repeated for images with artifacts, including decentration and defocus.

TCD Procedures

Participants were directed to Bezmialem University Faculty of Medicine Neurology Clinic for neurological

TABLE 1. Characteristics of the Patient and Control Groups

	Controls (N = 30)	POAG (N = 30)	OHT (N = 30)	*P*
Age (y)	57.5 ± 7.1	59.3 ± 6.7	58.6 ± 6.4	0.461*
Age range (y)	42-65	44-65	40-65	
Female sex, n (%)	18 (60.0)	19 (63.3)	22 (73.3)	0.529†
Systolic pressure (mm HG)	122.2 ± 10.9	117.0 ± 13.9	121.7 ± 15.6	0.146*
Diastolic pressure (mm HG)	70.5 ± 8.6	70.3 ± 8.8	67.3 ± 10.1	0.433*
IOP (mm HG)	15.3 ± 2.7	16.20 ± 4.8	20.2 ± 4.8	< 0.001*
CCT (μm)	541.5 ± 25.4	535.2 ± 36.1	557.8 ± 37.2	0.028*

Data are expressed as mean ± SD, except for sex.
*Kruskal-Wallis test.
†χ^2 test for differences among the 3 groups.
CCT indicates central corneal thickness; IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

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TABLE 2. Comparison of Structural and Functional Parameters Between the Patient and Control Groups

	Controls	POAG	*P**	OHT	*P*†
RNFL parameters (μm)					
Average	102.73 ± 13.25	77.70 ± 17.14	< 0.001	100.20 ± 9.17	0.375
Superior	104.40 ± 16.45	79.26 ± 16.44	< 0.001	102.07 ± 14.25	0.482
Inferior	103.17 ± 14.01	79.46 ± 19.51	< 0.001	100.40 ± 12.86	0.695
GCC parameters (μm)					
Average	94.03 ± 8.12	75.30 ± 12.76	< 0.001	93.70 ± 8.76	0.953
Superior	95.60 ± 8.34	75.90 ± 12.96	< 0.001	94.20 ± 10.7	0.292
Inferior	95.57 ± 8.49	71.40 ± 12.24	< 0.001	95.23 ± 10.3	0.679
Visual field parameters (dB)					
MD	−0.59 ± 0.85	−4.70 ± 1.81	< 0.001	−0.87 ± 0.90	0.258
PSD	1.62 ± 0.48	5.27 ± 1.61	< 0.001	1.57 ± 0.49	0.701

Data are presented as the mean ± SD.
*Controls versus the POAG group.
†Controls versus the OHT group (Mann-Whitney U test).
GCC indicates ganglion cell complex; MD, mean deviation; OHT, ocular hypertension; POAG, primary open-angle glaucoma; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer.

examinations and TCD ultrasonography. The investigators were blinded to group allocation until analyses had been completed.

The subjects were asked to rest for at least 30 minutes before the procedure to ensure cardiovascular stability. TCD ultrasonography examination was performed by an experienced investigator (E.G.) between 08:30 and 10:00 in a quiet room. Blood pressure and heart rate were simultaneously monitored (GE B30 Medical System, Freiberg, Germany). The ipsilateral MCA was evaluated through the temporal bone window with a 2-MHz probe while the participant was in a supine position. The MCA was visualized at depths between 45 and 55 mm from the temporal scalp. After the vascular structure was determined, the recording was started by fixing the probe. To evaluate the mean arterial BFV, the patients rested for ~10 minutes, following which they underwent a 5-minute record, which was performed after fixation of the probe. Patients were informed as necessary to provide cooperation; they were asked to hold their breath for 30 seconds after each 5-minute rest interval to calculate their BHI.[19] This process was repeated 3 times with a 5-minute interval. The maximal point of the mean blood flow was determined after the first inspiration following a standard 30-second breath holding. In the BHI study, the following equation was used: [(Vapnea–Vresting)/Vrestin)]×100/s, where Vapnea was the mean BFV of the vessel at the end of each period of breath holding, Vresting was the mean BFV of the vessel at rest, and per second (/s) was used to imply breaths held per second. Mean BFV and BHI measurements were made offline.

TABLE 3. Comparison of Cerebral Hemodynamics Between Patient and Control Groups

	Controls	POAG	*P**	OHT	*P*†
MCA mean BFV (cm/s)	58.50 ± 12.85	50.94 ± 10.95	0.007	59.02 ± 10.15	0.594
MCA BHI	1.19 ± 0.60	0.86 ± 0.44	0.019	1.18 ± 0.56	0.824

Data are presented as the mean ± SD.
*Controls versus the POAG group.
†Controls versus the OHT group (Mann-Whitney U test).
BFV indicates blood flow velocity; BHI, breath-holding index; MCA, middle cerebral artery; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY). The descriptive data are presented as the mean and SD, range, or ratio, as appropriate. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Differences in the distribution of demographic characteristics were compared between the 3 groups using the Kruskal-Wallis test or the χ^2 test. Cerebral hemodynamic parameters, OCT data, and visual field parameters of normal eyes were compared with those of the OHT and POAG eyes by the Mann-Whitney U test. A *P*-value of <0.05 was considered reflective of statistical significance.

RESULTS

The demographic and clinical characteristics of the participants are shown in Table 1. All participants in the study were between the ages of 40 and 65 years. There was no difference in the age or sex distribution among patients with POAG, OHT, and controls (all $P > 0.05$).

Table 2 shows the ocular parameters in the 3 studied groups. The mean visual field loss was significantly higher in the POAG group (−4.70 ± 1.81 dB) than in the controls (−0.59 ± 0.85 dB). The visual field test results were not statistically significantly different between patients with OHT (−0.87 ± 0.90 dB) and controls. Patients with POAG showed a significantly thinner mean peripapillary RNFL and macular GCC than control subjects (all $P < 0.001$). Patients with OHT and control subjects had similar mean peripapillary RNFL and macular GCC thicknesses.

Comparisons of mean BFV and BHI values between patients and controls are shown in Table 3. The BHI was 0.86 ± 0.44 in patients with POAG, 1.18 ± 0.56 in patients with OHT, and 1.19 ± 0.60 in the control group. The mean BFV and BHI of the MCAs were significantly lower in the POAG group (all $P < 0.05$) than they were in the control group. There were no significant differences in the mean BFV and BHI values between the OHT and control groups (Fig. 1).

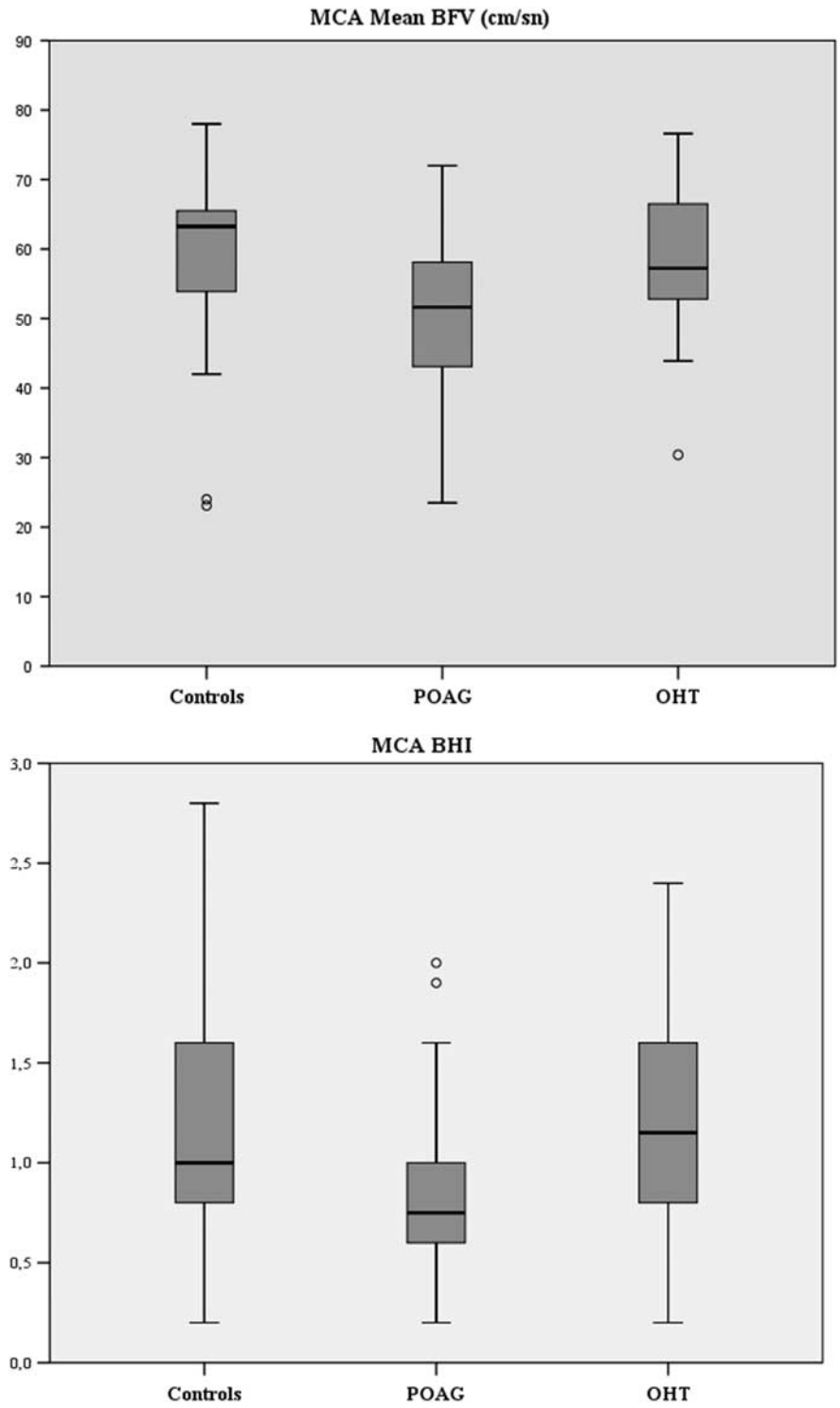

FIGURE 1. Box plot diagrams showing MCA BFV (top) and MCA BHI (bottom) of patients and age- and sex-matched controls. BFV indicates blood flow velocity; BHI, Breath-Holding Index; MCA, middle cerebral artery; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

DISCUSSION

In our study of patients without systemic cardiovascular or central nervous system disorders, BHI values and mean BFV in the MCAs were lower in patients with POAG than in control subjects. This impaired cerebral vascular regulation may contribute to an increased risk of stroke in patients with POAG. However, there were no significant differences in the mean BFV and BHI values between in patients with OHT and control individuals.

Differences in the distribution of CBF occurs in response to changes in partial arterial CO_2 pressure with a stimulus such as hypercapnia.[27,28] Assessment of this CVMR provides information about the adaptability of cerebral vessels in response to metabolic activity in the brain that requires an increase or a decrease in blood flow velocity. The decrease in CVMR could be associated with increased susceptibility to ischemic stroke.[29,30] In observational cohort studies, it was found that the risk of stroke development in patients with open-angle glaucoma was significantly higher than in control subjects. In these studies, the potential pathophysiological link between open-angle glaucoma and stroke could not be precisely explained; however, patients over 65 years of age, male individuals, and those with comorbid diseases, such as hypertension and diabetes, were more susceptible to stroke.[7,8]

Because of the high prevalence of vasospastic disorders in patients with glaucoma, impaired regulation of vascular resistance has already been associated with glaucoma.[31] Insufficient blood supply to the choroid, retina, and optic nerve head has been previously reported in POAG.[32] The optic nerve is a continuation of the central nervous system and shares many physiological similarities with the brain, including autoregulation of blood flow.[33] Duncan and colleagues assessed resting CBF in the primary visual cortex of patients with POAG using arterial spin-labeling functional magnetic resonance imaging. They found that the resting CBF was low in the primary visual cortex of these patients with POAG.[34] Zhang and colleagues showed that there was significantly lower blood flow in the posterior cerebral artery of 13 patients with POAG as compared with the control group. In addition, they suggested that POAG patients may have a cerebral vascular insufficiency in the posterior cerebral artery.[35] In another study of 16 patients with POAG, the BFVs in the MCA of these patients were lower than that in the MCA of control individuals.[36] These findings are consistent with our results, which show lower CBF velocities in patients with POAG compared with the control group.

Previous studies reported that CBF decreases in response to hyperoxia.[37,38] In addition, normal cerebral circulation autoregulates oxygen delivery by vasoconstriction in parallel with an increase in the arterial oxygen content.[39] In a study by Harris and colleagues, patients with glaucoma showed abnormal cerebrovascular responses to hyperoxia. In healthy controls, 100% oxygen breathing decreased MCA mean and peak BFVs; however, in patients with glaucoma, these velocities did not decrease. This finding showed that supplying oxygen to the brain is not well-regulated in patients with glaucoma.[36] In studies investigating cerebrovascular responses to hyperventilation, CBF velocity changes were significantly smaller in patients with glaucoma than in controls.[24,35] In this study, we evaluated CVMR to hypercapnia in response to breath holding in patients with POAG and found that patients with POAG had decreased vasodilation responses to hypercapnia.

The mechanism of the insufficient CVMR of the MCAs in patients with POAG remains unclear. The glial cells and surrounding neurons in the brain mediate the vasodilation and vasoconstriction of cerebral blood vessels through a neurovascular coupling. It has been suggested that neuronal activation plays an important role in CBF control based on an in vivo study in adult rats.[40] It is possible that these neuronal and glial changes in patients with glaucoma[41–44] may impair the regulation of arteries and may cause functional insufficiency of arterial vasoreactivity. In addition, impairment of peripheral endothelium-mediated vasodilatation was shown in patients with glaucoma.[45] Furthermore, altered endothelium-mediated vasoconstriction was present in these patients.[46] These findings suggest the presence of generalized vascular endothelial dysfunction in patients with glaucoma. Consequently, neuronal and glial changes and dysfunction of the vascular endothelium might be factors responsible for decreased vasodilation responses to hypercapnia in patients with POAG.

To the best of our knowledge, no previous study has investigated cerebral vasoreactivity with the BHI in patients with POAG or OHT. Vernieri and colleagues studied the outcomes of BHI in the MCA using TCD ultrasonography in 65 patients with internal carotid artery occlusion. They suggested that impaired CVMR with low BHI values is predictive for cerebral ischemic events in patients with internal carotid occlusion.[17] In a case-control study of 46 patients with lacunar infarction, the hemodynamics of MCAs were investigated using TCD ultrasonography. The results suggested that impaired cerebrovascular reactivity is a risk marker for first-ever lacunar infarction.[47] These studies confirm an association between a low BHI value and a high risk of stroke. Therefore, in this study, when compared with the control group, lower BHI values in patients with POAG may be associated with increased stroke risk.

It was previously reported that the development of POAG in a group of patients with OHT could not be prevented at the end of 60 months despite the IOP-lowering treatment.[10] In this study, we examined patients with OHT as this is closely related to glaucoma, and CVMR was not previously evaluated in this population. In our study, mean BFV values in patients with OHT were not significantly different from those in the control group. This finding was consistent with the study of Akarsu et al[48] on 24 patients with OHT. Moreover, we did not find any significant difference in the CVMR in terms of the BHI of patients with OHT compared with the control group. The lack of statistically significant differences in the mean BFV and BHI values between the OHT and control groups may be because of the small sample size. In addition, we speculate that patients with OHT may not have cerebral vascular autonomic dysfunction.

There are some potential limitations to this study. First, patients with late-stage glaucoma and those not in the age range of 40 to 65 years were not included. It is unclear how these results would change in patients with severe glaucoma or those aged older than 65 years. Second, as in previous studies investigating autonomic dysfunction in glaucoma, we restricted the withdrawal of the use of topical medications for 3 days for ethical reasons because discontinuation of topical medications can cause a significant increase in IOP, even after 24 hours.[24,49] However, the effect of topical glaucoma medication on our results can be neglected as the plasma concentration is low and decreases within several hours after application.[24] The current findings should also be confirmed by further studies involving more participants.

In conclusion, we found an impaired vasodilator response to hypercapnia in patients with POAG. Vasoreactivity changes in the MCA in patients with POAG may be secondary to neuronal and glial changes, or they may be the result of dysfunction of the vascular endothelium. Thus, impairment of the cerebral vascular regulation may contribute to the increased risk of stroke in patients with POAG.

REFERENCES

1. Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. *JAMA*. 2003;290: 2057–2060.
2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90: 262–267.
3. Yang Y, Yu M, Zhu J, et al. Role of cerebrospinal fluid in glaucoma: pressure and beyond. *Med Hypotheses*. 2010;74: 31–34.
4. Chopra V, Varma R, Francis BA, et al. Type 2 diabetes mellitus and the risk of open-angle glaucoma the Los Angeles Latino Eye Study. *Ophthalmology*. 2008;115:227–232.e1.
5. Tielsch JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch Ophthalmol*. 1995;113: 216–221.
6. Wilson MR, Hertzmark E, Walker AM, et al. A case-control study of risk factors in open angle glaucoma. *Arch Ophthalmol*. 1987;105:1066–1071.
7. Rim TH, Lee SY, Bae HW, et al. Increased stroke risk among patients with open-angle glaucoma: a 10-year follow-up cohort study. *Br J Ophthalmol*. 2018;102:338–343.
8. Lee WJ, Jeoung JW, Na KI, et al. Relationship between open-angle glaucoma and stroke: a 2010 to 2012 Korea National Health and Nutrition Examination Survey. *J Glaucoma*. 2018; 27:22–27.
9. van Gestel A, Webers CA, Beckers HJ, et al. Ocular hypertension and the risk of blindness. *J Glaucoma*. 2015;24: 9–11.
10. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701–830.
11. Gordon MO, Beiser JA, Brandt JD, et al. The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002; 120:714–830.
12. Flammer J, Orgül S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retinal Eye Res*. 2002;21: 359–393.
13. Wang Q, Chen W, Qu X, et al. Reduced cerebral blood flow in the visual cortex and its correlation with glaucomatous structural damage to the retina in patients with mild to moderate primary open-angle glaucoma. *J Glaucoma*. 2018;27: 816–822.
14. Garhöfer G, Fuchsjäger-Mayrl G, Vass C, et al. Retrobulbar blood flow velocities in open angle glaucoma and their association with mean arterial blood pressure. *Invest Ophthalmol Vis Sci*. 2010;51:6652–6657.
15. Glodzik L, Randall C, Rusinek H, et al. Cerebrovascular reactivity to carbon dioxide in Alzheimer's disease. *J Alzheimers Dis*. 2013;35:427–440.
16. Smoliński Ł, Członkowska A. Cerebral vasomotor reactivity in neurodegenerative diseases. *Neurol Neurochir Pol*. 2016;50: 455–462.
17. Vernieri F, Pasqualetti P, Passarelli F, et al. Outcome of carotid artery occlusion is predicted by cerebrovascular reactivity. *Stroke*. 1999;30:593–598.
18. Yonas H, Smith HA, Durham SR, et al. Increased stroke risk predicted by compromised cerebral blood flow reactivity. *J Neurosurg*. 1993;79:483–489.
19. Markus HS, Harrison MJ. Estimation of cerebrovascular reactivity using transcranial Doppler, including the use of breath-holding as the vasodilatory stimulus. *Stroke*. 1992;23: 668–673.
20. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA*. 2000;283: 2122–2127.
21. Herrera CR, Beltramini GC, Avelar WM, et al. Cerebral vasomotor reactivity assessment using transcranial Doppler and MRI with apnea test. *Braz J Med Biol Res*. 2016;49:e5437.
22. Topcuoglu MA, Chan ST, Silva GS, et al. Cerebral vasomotor reactivity in reversible cerebral vasoconstriction syndrome. *Cephalalgia*. 2017;37:541–547.
23. Placidi F, Diomedi M, Cupini LM, et al. Impairment of daytime cerebrovascular reactivity in patients with obstructive sleep apnoea syndrome. *J Sleep Res*. 1998;7:288–292.
24. Tutaj M, Brown CM, Brys M, et al. Dynamic cerebral autoregulation is impaired in glaucoma. *J Neurol Sci*. 2004;220: 49–54.
25. Negri L, Ferreras A, Iester M. Timolol 0.1% in glaucomatous patients: efficacy, tolerance, and quality of life. *J Ophthalmol*. 2019;2019:4146124.
26. Denis P, Covert D, Realini A. Travoprost in the management of open-angle glaucoma and ocular hypertension. *Clin Ophthalmol*. 2007;1:11–24.
27. Ainslie PN, Duffin J. Integration of cerebrovascular CO_2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol*. 2009;296:R1473–R1495.
28. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2:161–192.
29. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann Neurol*. 1991;29:231–240.
30. Oz O, Tasdemir S, Akgun H, et al. Decreased cerebral vasomotor reactivity in patients with obstructive sleep apnea syndrome. *Sleep Med*. 2017;30:88–92.
31. Broadway DC, Drance SM. Glaucoma and vasospasm. *Br J Ophthalmol*. 1998;82:862–870.
32. Fuchsjäger-Mayrl G, Wally B, Georgopoulos M, et al. Ocular blood flow and systemic blood pressure in patients with primary open-angle glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci*. 2004;45:834–839.
33. Flammer J, Orgül S. Optic nerve blood-flow abnormalities in glaucoma. *Prog Retinal Eye Res*. 1998;17:267–289.
34. Duncan RO, Sample PA, Bowd C, et al. Arterial spin labeling fMRI measurements of decreased blood flow in primary visual cortex correlates with decreased visual function in human glaucoma. *Vision Res*. 2012;60:51–60.
35. Zhang S, Xie Y, Yang J, et al. Reduced cerebrovascular reactivity in posterior cerebral arteries in patients with primary open-angle glaucoma. *Ophthalmology*. 2013;120: 2501–2507.
36. Harris A, Zarfati D, Zalish M, et al. Reduced cerebrovascular blood flow velocities and vasoreactivity in open-angle glaucoma. *Am J Ophthalmol*. 2003;135:144–147.
37. Omae T, Ibayashi S, Kusuda K, et al. Effects of high atmospheric pressure and oxygen on middle cerebral blood flow velocity in humans measured by transcranial Doppler. *Stroke*. 1998;29:94–97.
38. Watson NA, Beards SC, Altaf N, et al. The effect of hyperoxia on cerebral blood flow: a study in healthy volunteers using magnetic resonance phase-contrast angiography. *Eur J Anaesthesiol*. 2000;17:152–159.
39. Armstead WM. Endothelin-1 contributes to normocapnic hyperoxic pial artery vasoconstriction. *Brain Res*. 1999;842: 252–255.
40. Zonta M, Angulo MC, Gobbo S, et al. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat Neurosci*. 2003;6:43–50.
41. Boucard CC, Hernowo AT, Maguire RP, et al. Changes in cortical grey matter density associated with long-standing retinal visual field defects. *Brain*. 2009;132(Pt 7):1898–1906.
42. Gupta N, Ang LC, Noël de Tilly L, et al. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. *Br J Ophthalmol*. 2006;90: 674–678.
43. Lam D, Jim J, To E, et al. Astrocyte and microglial activation in the lateral geniculate nucleus and visual cortex of glaucomatous and optic nerve transected primates. *Mol Vis*. 2009;15:2217–2229.

44. Zhang S, Wang H, Lu Q, et al. Detection of early neuron degeneration and accompanying glial responses in the visual pathway in a rat model of acute intraocular hypertension. *Brain Res*. 2009;1303:131–143.
45. Henry E, Newby DE, Webb DJ, et al. Peripheral endothelial dysfunction in normal pressure glaucoma. *Invest Ophthalmol Vis Sci*. 1999;40:1710–1714.
46. Buckley C, Hadoke PW, Henry E, et al. Systemic vascular endothelial cell dysfunction in normal pressure glaucoma. *Br J Ophthalmol*. 2002;86:227–232.
47. Molina C, Sabín JA, Montaner J, et al. Impaired cerebrovascular reactivity as a risk marker for first-ever lacunar infarction: a case-control study. *Stroke*. 1999;30:2296–2301.
48. Akarsu C, Bilgili YK, Unal B, et al. Cerebral hemodynamics in ocular hypertension. *Graefes Arch Clin Exp Ophthalmol*. 2005;243:317–320.
49. Brown CM, Dütsch M, Michelson G, et al. Impaired cardiovascular responses to baroreflex stimulation in open-angle and normal-pressure glaucoma. *Clin Sci*. 2002;102:623–630.