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Original Article

Ocular rigidity and neuroretinal damage in patients with vasospasticity: a pilot study

Diane N Sayah,*,† Javier Mazzaferri,* Denise Descovich,* Santiago Costantino,*,†,‡ Mark R Lesk*,†,‡

Objective: Evidence suggests that ocular blood flow dysregulation in patients with vasospasticity could occur in response to biomechanical stimuli, contributing to optic nerve head susceptibility in glaucoma. We evaluate the role of vasospasticity in the association between ocular rigidity (OR) and neuroretinal damage, hypothesizing that low OR correlates with greater glaucoma damage in patients with vasospasticity.

Design: Cross-sectional study.

Participants: Patients with open-angle glaucoma (OAG), suspect discs, or no glaucoma.

Methods: OR was measured using a noninvasive, validated method developed by our group. Retinal nerve fibre layer (RNFL) and ganglion cell complex thicknesses were acquired using spectral domain optical coherence tomography. Vasospasticity was assessed by a standardized questionnaire that was based on existing validated questionnaires and adapted to our requirements. Atherosclerosis was evaluated based on Broadway and Drance's (1998) cardiovascular disease score. Correlations between OR and structural parameters were assessed in patients with vasospasticity and those with atherosclerosis.

Results: Of 118 patients with either OAG (n = 67), suspect discs (n = 26), or no glaucoma (n = 25) who were recruited consecutively, 10 were classified as having vasospasticity, and 37 as having atherosclerosis. In the vasospastic group, significant correlations were found between OR and the minimum ganglion cell complex thickness ($r_s = 0.681$, $p = 0.030$), the average RNFL thickness ($r_s = 0.745$, $p = 0.013$), and the RNFL in the temporal quadrant ($r_s = 0.772$, $p = 0.009$), indicating more damage with lower OR. Similar trends were maintained when applying multiple testing correction; however, only the eighth RNFL clock hour corresponding to the inferior-temporal peripapillary region remained significantly correlated with OR in the vasospastic group ($p = 0.015$). In contrast, no correlation was found in the atherosclerotic group ($p > 0.05$).

Conclusions: The findings of the current pilot study indicate a trend for more neuronal structural damage in less-rigid eyes of patients with vasospasticity, meaning that OR may play a greater role in glaucoma in vasospastic patients than in patients with atherosclerosis. Although these results provide interesting insight into the pathophysiology of OAG, further investigation is needed to confirm our observations.

Open-angle glaucoma (OAG) is an ocular disease characterized by structural damage to retinal ganglion cells (RGC) and axons that compose the optic nerve, resulting in visual field loss and leading to blindness. This disease is known to be multifactorial. The main mechanisms thought to explain the pathogenesis of this blinding disease include the mechanical and vascular theories. The first postulates that elevated mechanical stress and strain lead to axonal damage and RGC loss.[1–3] An individual's predisposition to develop glaucoma may depend on eye-specific geometrical and material properties, such as ocular rigidity (OR). The second theory proposes reduced ocular perfusion pressure and vascular dysregulation as the main culprits leading to the optic neuropathy.[4–6] These mechanisms, however, are probably not mutually exclusive, but rather intertwined. It is hypothesized that ocular biomechanics along with other processes in the eye can influence blood flow.[7]

OR is an important biomechanical parameter representing the resistance that the eye exerts to distending forces. Finite element modeling suggests that scleral stiffness, the main contributor to OR, could be the most important biomechanical factor in determining strain at the optic nerve head (ONH), perhaps more so than intraocular pressure (IOP).[8,9] A more compliant sclera would lead to increased ONH strain (deformation) levels and more neuronal damage. A recent clinical study by our group showed that low OR is correlated with greater glaucomatous neuroretinal damage in a large cohort that included eyes across the glaucoma spectrum.[10]

Vasospasticity, or primary vascular dysregulation (PVD), is characterized by the body's abnormal response to stimuli such as temperature and emotional stress, leading to cold extremities.[11] Vasospasticity is a risk factor for glaucoma[12–15] and renders the eye more susceptible to damage in response to IOP or ocular perfusion pressure (OPP) changes due to defective autoregulation.[11] An example of this is shown by Hafez et al.,[16] who reported that after therapeutic IOP reduction in patients with OAG there were significantly greater increases in neuroretinal rim blood flow in patients with vasospasticity compared to non-vasospastic patients, indicating defective autoregulation in these patients. Furthermore, evidence suggests that patients with PVD could present ocular blood flow dysregulation in response to biomechanical stimuli, contributing to the ONH's susceptibility in glaucoma.[14,17–20] A landmark paper from Stephen Drance's laboratory showed a strong

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correlation between biomechanics (in the form of Tmax [maximal known IOP]) and visual field damage in vasospastic glaucoma patients, a correlation that was absent in patients with atherosclerosis.[18]

In the current study, we aim to evaluate the role of vasospasticity in the association between OR and neuroretinal damage. We hypothesize that OR will be more closely correlated with the degree of glaucoma damage in subjects with a concurrent vasospastic syndrome.

Materials and methods

This study followed the tenets of the Declaration of Helsinki and was approved by the Maisonneuve-Rosemont Hospital institutional review board. Informed consent was obtained from all participants prior to testing.

OR was measured using a noninvasive method.[21,22] Briefly, this method involves the measurement of the pulsatile ocular volume change using dynamic optical coherence tomography (OCT) imaging, coupled with a custom segmentation algorithm, and the pulsatile IOP change using the Pascal tonometer.[21] This noninvasive methodology has been previously validated against an invasive procedure. A strong correlation (r_s=0.853, p<0.001) was found between OR coefficients obtained in a same eye using the noninvasive method and the invasive procedure, which involved intravitreal injections and IOP spike measurement.[22] The optical method was also shown to have good repeatability.[22] The OR coefficient was then computed using Friedenwald's equation.[23] Structural OCT-based parameters, including neuroretinal rim area, macular ganglion cell complex (GCC), and retinal nerve fibre layer (RNFL) thicknesses, were acquired using the Cirrus 5000 OCT (Carl Zeiss Meditec AG, Dublin, Calif., USA).

Adult participants with suspect discs or primary OAG were recruited from the Hôpital Maisonneuve-Rosemont (HMR) Ophthalmology Glaucoma Clinic. Volunteers with healthy eyes were recruited from older subjects consulting in theHMR Ophthalmology clinic for disorders such as blepharitis, which are not thought to be related to altered OR. Recruitment was carried out sequentially and directly by the research team from patients consulting in the clinic. A complete ocular examination was performed for all participants. Healthy participants had IOP less than 21 mm Hg under no pharmacological treatment, normal optic nerve appearance on fundus exam, normal visual fields, and no other ocular disease. Participants with suspect discs had increased cup-to-disc ratio or asymmetry of optic nerve appearance, with no detectable functional or structural damage. IOP in this group could be within normal range or elevated, and if there was a history of elevated IOP, could be treated with topical IOP-lowering agents. Participants with OAG had open (nonoccludable) angles on gonioscopy, a glaucomatous optic nerve appearance, as well as repeatable structural and/or functional findings with OCT imaging and/or Humphrey visual field (VF) testing (Zeiss Humphrey Systems, Dublin, Calif., USA; Swedish Interactive Threshold Algorithm Standard 24−2 strategy). Patients with preperimetric glaucoma who had confirmed neuroretinal damage were included in the glaucoma group. Participants were required to have clear media, steady fixation, and the ability to fixate a target light with the study or contralateral eye. Patients with a previous history of intraocular surgery (except remote phacoemulsification/intraocular lens implantation), including trabeculectomy, tube shunt, and refractive surgery, were excluded. Other exclusion criteria included secondary glaucoma, non-glaucomatous optic neuropathy, any retinopathy, documented systemic collagen disease, and concomitant pathologies that could affect the visual field. Participants in this study form a subset of patients from another larger study.[10]

All participants were questioned about their systemic health, and medical records were reviewed. Brachial systolic and diastolic blood pressures were recorded for each subject while seated using an automatic sphygmomanometer device (Welch Allyn Inc., Skaneateles Falls, NY). Vasospasticity, atherosclerosis, and other vascular risk factors were assessed by a questionnaire based on similar studies.[24−28] The questionnaire developed and used in this study is shown in Figure 1. Participants were divided into the vasospastic group and atherosclerotic group, according to the collected data as summarized in Table 1. Participants were considered vasospastic if they answered positively to questions 1, 2, or 3. An "overall cardiovascular disease score" was calculated for each patient, where the five elements considered were hypertension, ischemic heart disease, cerebral ischemic disease, and diabetes and/or hemodynamic crisis.[24] A score greater or equal to 1/5 indicated the presence of vascular disease or atherosclerosis (question 4). Questions 5 and 6 served to confirm the latter. Questions 7 through 9 were not analyzed in the current study.

Statistical analyses were performed using SPSS statistical software (version 26.0; IBM Corp, Armonk, NY). Descriptive analysis of baseline demographics was carried out and presented as the mean ± standard deviation. To compare the vasospastic and atherosclerotic groups, a t test, or equivalent based on distribution and equality of variances assessment, or χ^2 test was used where applicable. Correlations between OR and structural parameters were assessed in the two groups of participants for comparison. The False Discovery Rate approach was used to correct for multiple testing.[29] For all statistical tests, a p value inferior to 0.05 was considered significant.

Results

Forty-seven subjects were included in this study. Out of 118 subjects recruited consecutively for a previous study,[10]

QUESTIONNAIRE (FOR INVESTIGATOR'S USE) Date: ____ /____ /____

Developed by Sayah DN, et al., (2022)

Glaucoma Research Laboratory, University of Montreal, QC, Canada

Patient ID: _____ Name : _____ Date of Birth: _____

1. Do you have cold hands or feet (possibly also in the summer) or have other people ever told you that your hands are cold?
    - Are your hands or feet cold when other people's are not?
2. Do your fingers change color when they are exposed to cold temperature?
    - Do they turn white, blue, or both?
3. Do you suffer from migraines?

    If answer is positive, refer to the International Headache Society Diagnostic criteria to confirm.
4. Do you have a history of cardiovascular diseases? (score __ / 5)
    - Hypertension?
    - Diabetes? Type I / II / gestational
    - Ischemic heart disease? Angina, infarction, valve problem, arrythmia
    - Cerebral ischemic disease? Stroke, transient ischemic attack
    - Hemodynamic crisis? Blood loss, transfusion, heart stoppage
5. What medication do you take? Ask for list.
    - Ask specifically for blood pressure (calcium channel blockers), cholesterol, diabetes (per os, insulin), heart medication, estrogen replacement therapy
    - Other
6. Do you smoke?
    - Smoker/ ex-smoker / non-smoker
        - Duration of smoking (years)?
        - Average daily number of cigarettes (or other) smoked?
7. What is your height and weight?
    - Calculate the body mass index
8. Do you suffer from sleep apnea? (refer to the STOP-BANG questionnaire)
9. Caffeine / Alcohol consumption:
    - How many cups of caffeinated beverage do you drink every day?
    - How many alcoholic beverages do you drink every day? (more or less than 7 oz)

Fig. 1—Questionnaire developed to establish the presence of vasospasticity, cardiovascular diseases, and other vascular risk factors. (Modeled after the International Headache Society Diagnostic criteria,[26] STOP-BANG screening questionnaire for obstructive sleep apnea,[27,30] and body mass index calculation.[31])

Table 1—Description of the inclusion and exclusion criteria for the vasospastic and atherosclerotic groups based on participants' answers to the questionnaire.

	Vasospastic Group	Atherosclerotic Group
Question 1 "cold hands or feet"	Yes*	No
Question 2 "fingers change color"	Yes*	No
Question 3 "migraines"	Yes*	No
Question 4 "cardiovascular diseases" (score on 5)	Score 0/5	Score ≥ 1/5

*A subject who answered positively to Questions 1, 2, or 3 was considered vasospastic.

10 only had vasospasticity (without atherosclerosis), and 37 only had atherosclerosis (without vasospasm and/or migraine). Excluded subjects included 20 who had both vasospasticity and atherosclerosis, 34 who had neither, and 17 who did not answer the questionnaire. Of the 47 participants, 26 (55%) were male, 39 (83%) were White, 7 (15%) were of African descent, and 1 (2%) was Hispanic. One eye per subject was included; 25 (53%) were right eyes. Twenty-eight subjects had early to moderate OAG, 11 had suspect discs, and 8 were healthy (no glaucoma). The baseline characteristics of all included participants are shown in Table 2. The assumption of homogeneity of variance was respected for all variables following the Levene Test for Equality of Variances ($p>0.05$). Owing to unequal sample size and non-normal distribution, a Mann-Whitney U test and χ^2 test were carried out. The Spearman correlations between OR and parameters of neuroretinal damage in the vasospastic group and atherosclerotic group are shown in Table 3. In the vasospastic group, significant correlations were found between OR and the minimum GCC thickness ($r_s = 0.681$, $p = 0.030$), average RNFL thickness ($r_s = 0.745$, $p = 0.013$), and the RNFL in the temporal quadrant ($r_s = 0.772$, $p = 0.009$), indicating more damage with lower OR. In contrast, no correlation was found in the atherosclerotic group ($r_s = 0.219$, $p = 0.282$; $r_s = 0.190$, $p = 0.261$; and $r_s = 0.179$, $p = 0.319$ respectively). Similarly, no significant correlations were found between OR and parameters of neuroretinal damage in 20 participants with concomitant vasospasticity and atherosclerosis ($r_s = -0.080$, $p = 0.769$; $r_s = -0.293$, $p = 0.211$; and $r_s = -0.358$, $p = 0.121$ respectively).

After correcting for multiple testing, similar trends were maintained between structural parameters indicating glaucomatous damage and OR in the vasospastic group; however, only the eighth clock hour corresponding to the inferior-temporal region of the RNFL remained statistically significantly correlated with OR ($p = 0.015$). No such correlation was found in the atherosclerotic group ($p > 0.05$). Figures 2 and 3 display the relationship between OR coefficients and neuroretinal damage parameters in the vasospastic group and the atherosclerotic group respectively.

Table 2—Baseline demographics and clinical characteristics of participants in the vasospastic and atherosclerotic groups.

	Vasospastic Group (n = 10)	Atherosclerotic Group (n = 37)	*p* value
Eye (OD/OS)	4/6	21/16	0.279
Sex (M/F)	3/7	23/14	0.073
Ethnicity (White/Other)	8/2	31/6	0.550
Diagnosis (Healthy/Suspect/OAG)	2/1/7	6/10/21	0.591
History of Migraines	3	0	0.009
Age (years)	63±12	66±9	0.929
Systolic Blood Pressure (mm Hg)	124±23	134±19	0.050
Diastolic Blood Pressure (mm Hg)	77±9	80±7	0.203
Axial length (mm)	24.74±1.27	24.33±1.22	0.419
Tmax (mm Hg)	20±4	22±6	0.647
GAT-IOP (mm Hg)	16±4	17±4	0.476
DCT-IOP (mm Hg)	18.8±4.0	18.7±3.7	1.000
Ocular Pulse Amplitude (mm Hg)	2.9±1.3	3.0±1.3	0.692
Ocular Rigidity (μL^{-1})	0.026±0.015	0.023±0.013	0.711
Neuroretinal Rim Area (mm^2)	1.05±0.19	1.02±0.34	0.459
Average GCC Thickness (μm)	71±10	69±9	0.768
Minimum GCC Thickness (μm)	68±12	66±11	0.689
Average RNFL Thickness (μm)	80±15	79±13	0.828
Average RNFL Thickness (range) (μm)	57 to 106	49 to 107	—
Inferior Quadrant RNFL Thickness (μm)	96±26	101±20	0.600
Temporal Quadrant RNFL Thickness (μm)	57±18	58±12	0.356
Superior Quadrant RNFL Thickness (μm)	97±23	97±19	0.966
Sixth Clock Hour RNFL Thickness (μm)	103±36	108±29	0.487
Seventh Clock Hour RNFL Thickness (μm)	106±28	108±28	0.810
Eighth Clock Hour RNFL Thickness (μm)	62±27	58±14	0.524
Ninth Clock Hour RNFL Thickness (μm)	46±9	48±10	0.452
10th Clock Hour RNFL Thickness (μm)	64±19	67±17	0.435
11th Clock Hour RNFL Thickness (μm)	108±27	106±28	0.944
12th Clock Hour RNFL Thickness (μm)	97±31	96±25	0.788
Visual Field Mean Defect (dB)	-1.86±2.95	-2.35±3.41	0.722
Visual Field Mean Defect (range) (dB)	-7.38 to 0.00	-16.92 to 1.97	—

Data is presented as the mean ± standard deviation where applicable.
OAG, open-angle glaucoma; GAT, Goldmann applanation tonometry; IOP, intraocular pressure; DCT, dynamic contour tonometry; GCC, ganglion cell complex; RNFL, retinal nerve fibre layer.

Table 3—Comparison of the association between ocular rigidity and structural damage in glaucoma in the vasospastic group and atherosclerotic group. Spearman correlation coefficients and significance values are shown (in bold, if $p < 0.05$). Adjusted p values following multiple testing correction are shown in the columns to the right.

	Vasospastic Group	Atherosclerotic Group	Vasospastic Group (adjusted p-value)	Atherosclerotic Group (adjusted p-value)
Neuroretinal Rim Area	0.584 (0.077)	0.236 (0.173)	(0.128)	(0.603)
Average GCC Thickness	0.479 (0.162)	0.128 (0.532)	(0.203)	(0.665)
Minimum GCC Thickness	**0.681 (0.030)**	0.219 (0.282)	(0.108)	(0.603)
Average RNFL Thickness	**0.745 (0.013)**	0.190 (0.261)	(0.065)	(0.603)
Inferior Quadrant RNFL Thickness	0.418 (0.229)	0.148 (0.412)	(0.245)	(0.618)
Temporal Quadrant RNFL Thickness	**0.772 (0.009)**	0.179 (0.319)	(0.065)	(0.603)
Superior Quadrant RNFL Thickness	0.4500.192	-0.001 (0.994)	(0.222)	(0.998)
Sixth Clock Hour RNFL Thickness	0.596 (0.069)	0.114 (0.528)	(0.128)	(0.665)
Seventh Clock Hour RNFL Thickness	**0.661 (0.038)**	0.001 (0.998)	(0.108)	(0.998)
Eighth Clock Hour RNFL Thickness	**0.875 (0.001)**	0.027 (0.883)	**(0.015)**	(0.998)
Ninth Clock Hour RNFL Thickness	0.628 (0.052)	0.244 (0.171)	(0.111)	(0.603)
10^{th} Clock Hour RNFL Thickness	**0.648 (0.043)**	**0.350 (0.046)**	(0.108)	(0.603)
11^{th} Clock Hour RNFL Thickness	0.552 (0.098)	0.164 (0.362)	(0.134)	(0.603)
12^{th} Clock Hour RNFL Thickness	0.389 (0.266)	-0.230 (0.197)	(0.266)	(0.603)
Visual Field Mean Defect	0.685 (0.090)	0.163 (0.357)	(0.134)	(0.603)

GCC, ganglion cell complex; RNFL, retinal nerve fibre layer.

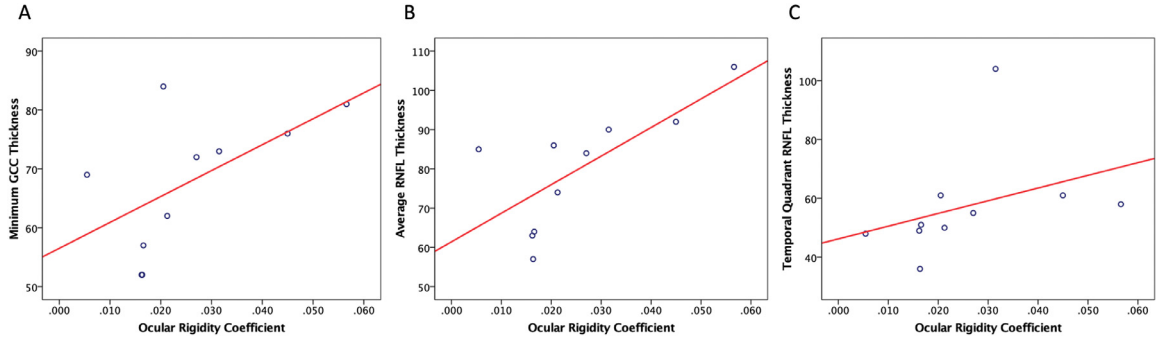

Fig. 2—Relationship between ocular rigidity coefficients and neuroretinal damage parameters in the vasospastic group. Scatter plots showing significant correlations between ocular rigidity coefficients and the A) minimum ganglion cell complex (GCC) thickness (r = 0.681, $p = 0.030$; GCC=56.51+440*OR); B) average retinal nerve fibre layer (RNFL) thickness (r = 0.745, $p = 0.013$; average RNFL = 61.42+729*OR); C) RNFL thickness in the temporal quadrant (r = 0.772, p = 0.009; temporal quadrant RNFL = 46.23+432*OR).

Discussion

In this pilot study, we found a correlation between OR and OCT-based parameters of neuroretinal damage in the vasospastic group, indicating more damage in eyes with lower OR (Table 3). Similar trends were maintained when applying multiple testing correction; however, only the eighth RNFL clock hour corresponding to the inferior-temporal peripapillary region remained statistically significantly correlated with OR in the vasospastic group ($p = 0.015$). This suggests a tendency for an association between low OR and greater neuroretinal damage in glaucoma in subjects with concurrent vasospasticity. In comparison, the atherosclerotic group showed no significant correlation between OR and these parameters, except for a weak positive correlation with RNFL in the 10^{th} clock hour, which was no longer significant after correction. Despite the small number of subjects, which limits statistical power, the results suggest two distinct subpopulations with distinct characteristics within the initial heterogeneous population. This corroborates the findings from Stephen Drance's laboratory,[18] which previously reported two distinct and statistically significantly different subgroups within a population of participants with low and high-tension glaucoma. In their study, the group with vasospasticity showed a positive correlation between the visual field mean defect and the maximum historic IOP (Tmax), indices of glaucomatous functional damage and biomechanics respectively. In contrast, the group with vascular disease, akin to atherosclerosis, showed no correlation between these variables. The authors argued that this finding may indicate the presence of different pathogenic mechanisms leading to glaucoma in these two groups. As such, they showed that the first group, although smaller (n = 15), may be more sensitive to the biomechanical environment in the eye, whereas the second, larger group (n = 45) presented disturbed coagulation and biochemical measurements consistent with ischemic

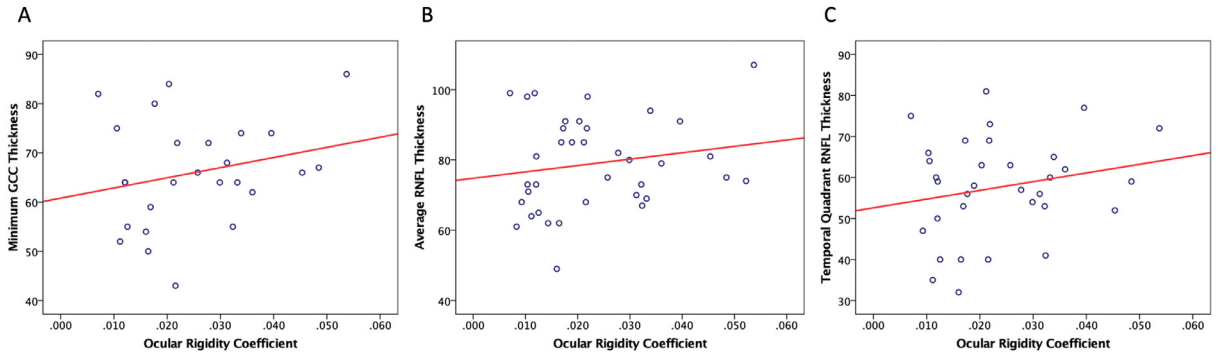

Fig. 3—Relationship between ocular rigidity coefficients and neuroretinal damage parameters in the atherosclerotic group. Scatter plots showing non-significant correlations between ocular rigidity coefficients and the A) minimum ganglion cell complex (GCC) thickness (r = 0.219, *p* = 0.282; GCC=60.81+206*OR); B) average retinal nerve fibre layer (RNFL) thickness (r = 0.190, *p* = 0.261; average RNFL = 74.77+182*OR); C) RNFL thickness in the temporal quadrant (r = 0.179, *p* = 0.319; temporal quadrant RNFL = 52.62+212*OR).

vascular disease, suggesting that ischemia may contribute to their glaucomatous damage.

Interestingly, we found a stronger correlation between Tmax and the visual field mean defect in the vasospastic group than in the atherosclerotic group, similar to Drance's findings, although this was not statistically significant. This may be because our cases had less advanced disease or may be due to a smaller sample size.

The positive correlation found between OR and the OCT-based parameters reflecting glaucomatous neuroretinal damage is consistent with our previous findings in a non-homogeneous population.[10] Our findings are also in agreement with several reports on the association between OR and OAG that show lower OR values in patients with glaucoma compared to controls,[32–34] including a much earlier study by Stephen Drance[24] as well as experimental studies[35] and finite element modeling, which suggest that a more compliant sclera is associated with increased strain at the ONH.[8,9,36]

We recognize some limitations of our study and that these should be addressed in future studies. The first limitation is the small size of the groups, particularly the vasospastic group, because single data points may have a large impact on the correlations and their interpretation. The group sizes must be increased to permit additional statistical testing (including adjusting for potential covariates), increase the statistical power, and strengthen the study's conclusions. It is interesting to note, however, that the proportion of vasospastic to atherosclerotic participants reported in the previous study (15 and 45) and in our study (10 and 37) is almost equivalent. Perhaps this may be representative of the proportion of vasospasticity in such a population. Another limitation is that the presence of both vasospasticity and atherosclerosis in our study was established by questioning the patient and through review of the medical records, as opposed to quantitative blood flow measurement after cold stimuli. Although it is based on validated and previously published questionnaires,[24–28] the questionnaire used in this study has not been validated integrally. Objective, quantitative measurements methods for vasospasticity include finger blood flow and nailfold capillaroscopy and should be used in future studies. Nevertheless, a number of studies have been published using only a questionnaire to establish the presence of vasospastic syndrome with seemingly good reliability without engaging in additional testing.[25,28,37] In a cohort of 123 patients, the subjective complaint of cold extremities was significantly correlated with objective peripheral vasospastic testing.[24] A pioneer in this field considered the brief verbal questionnaire and a handshake to be the gold standard against which quantitative testing for vasospasticity should be judged (S.M. Drance, personal communication, March 7, 1998). No hematological or biochemical measurements were carried out specifically for the purpose of this study.

Although the presence of migraines is thought to be a possible surrogate for vascular dysregulation,[28,38] not all vasospastic participants in this study reported a history of migraines. This is consistent with previous reports that not all patients with vasospastic syndrome suffer from migraine.[39]

Conclusion

Finally, our study demonstrates for the first time that OR and parameters of neuroretinal damage are correlated in subjects with vasospasticity, compared to those with ischemic vascular disease. In other words, these observations may indicate more structural damage in less-rigid eyes and perhaps that OR may play a greater role in this subgroup of patients with glaucoma. Vasospasticity, a known risk factor in glaucoma, may render the vasculature of the eye more susceptible to biomechanical stimuli, including IOP and its fluctuations. In clinical practice, this may translate into an increased benefit for therapeutic IOP-lowering in patients

with vasospasticity, especially those with lower OR. This may have been what was observed in the Canadian Glaucoma Study, where in *treated* patients vasospasticity was not found to be a risk factor for progression.[40] Although further investigation is warranted to confirm our results and to elucidate how low OR may play a greater role in certain subgroups of patients with glaucoma, these findings provide insight into the pathophysiology of OAG.

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Footnotes and Disclosure

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From the *Maisonneuve-Rosemont Hospital Research Centre, Montreal, QC; †Department of Ophthalmology, Université de Montréal, Montreal, QC; ‡Centre Universitaire d'Ophtalmologie (CUO), Maisonneuve-Rosemont Hospital, CIUSSS-E, Montreal, QC.

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Correspondence to Mark R Lesk, MD, MSc, Department of Ophthalmology, Université de Montréal, Maisonneuve-Rosemont Hospital Research Center, 5415 Blvd Assomption, Montreal, QC H1T 2M4 Canada. lesk@videotron.ca