

Ophthalmic Artery Doppler Waveform Changes Associated with Increased Damage in Glaucoma Patients

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PURPOSE. To characterize Doppler waveform variables (early systolic acceleration [ESA] and systolic/diastolic mean velocity ratios [Sm/Dm]) of the Ophthalmic Artery (OA) by color Doppler imaging (CDI) in eyes with primary open-angle glaucoma (POAG).

METHODS. Analysis of CDI examinations of the retrobulbar circulation of patients with POAG ($n = 102$), normal tension glaucoma (NTG, $n = 89$), and healthy controls ($n = 59$) by a condition-masked investigator. One-way ANOVA, chi-square, and Spearman's rank correlation tests were used to determine differences, establish comparisons, and to explore associations between variables, respectively.

RESULTS. The overall Doppler waveform presented a shift to the right in the glaucoma groups, with significantly lower Sm/Dm ratios when compared to the control group (healthy: 2.94 ± 0.86 , POAG: 2.60 ± 0.67 , NTG: 2.63 ± 0.84 ; $P = 0.01$). ESA was significantly lower in the glaucoma groups (healthy: $688.8 \pm 484 \text{ cm}\cdot\text{s}^{-2}$, POAG: $548.1 \pm 419 \text{ cm}\cdot\text{s}^{-2}$, NTG: $548.5 \pm 337 \text{ cm}\cdot\text{s}^{-2}$; $P = 0.03$). No statistical differences were, however, detected in the OA velocities or resistance index (P ranged between 0.08 and 0.96). In the glaucoma groups, waveform parameters such as ESA, acceleration time, and systolic mean velocities correlated with systemic blood pressure variables ($P < 0.05$). In these groups, negative correlations were detected between Sm/Dm ratios and the degree of visual field defects (POAG: $P = 0.01$; $r = -0.25$) and retinal nerve fiber layer thickness (NTG: $P = 0.02$; $r = -0.25$).

CONCLUSIONS. The pattern of blood flow velocities in the OA throughout the cardiac cycle seems to be altered in glaucoma patients. Further studies on how systemic blood pressure affects waveform variables in glaucoma patients may provide a better understanding of an underlying vascular dysfunction. (*Invest Ophthalmol Vis Sci.* 2012;53:2448-2453) DOI: 10.1167/iovs.11-9388

Primary open-angle glaucoma (POAG) is one of the most prevalent causes of irreversible blindness in the industrialized world.¹ The mainstay of current therapies has been to decrease the main modifiable risk factor: intraocular pressure

(IOP). However, and despite significant decreases in IOP, there are a significant number of patients that show signs of disease progression.^{2,3} The search for other risk factors has led to the identification of a number of vascular alterations in patients with glaucoma, especially the ones with an otherwise normal IOP (normal tension glaucoma, or NTG). Patients with glaucoma have been found to have an increased incidence of peripheral vasospasms,⁴ migraine,⁵ systemic hypotension⁶ and silent organ ischemia,⁷ in what has been suggested to be signals of a systemic vascular dysfunction. In the ocular circulation, a number of studies have used color Doppler imaging (CDI) technology to assess the retrobulbar arteries. Most of them have found reduced peak systolic velocities (PSV) and increased resistivity indices (RI) in the retrobulbar vessels of glaucoma patients when compared to healthy normal controls.⁸⁻¹¹ The vast majority of these studies have looked at only 3 variables: PSV, RI, and end-diastolic velocities (EDV) of the Doppler waveform of these arteries. In other medical specialties, however, much more information is usually retrieved from the analysis of the arterial waveforms. For example, the slope of the fastest-moving portion of the systolic component (early systolic acceleration, or ESA) and the time duration of that slope (acceleration time, or AT) have been extensively used in renal and hepatic arteries to identify changes in vascular lumen and altered distal resistance.^{12,13} These parameters have been clinically used to predict transplantation failures and detect significant arterial stenosis.¹⁴⁻¹⁶ Another aspect of the Doppler waveform is the ratio between the mean velocities of the systolic and diastolic components. This evaluation of the shift of blood flow velocities toward the beginning or the end of the cardiac cycle depends on both the arterial compliance and resistance characteristics.^{17,18} To the authors' best knowledge, none of the previous studies have performed any such analysis of the retrobulbar arteries of glaucoma patients. This study aims at further characterizing the ophthalmic artery's Doppler waveform in glaucoma patients, and to clarify whether any of these new variables can provide further insights on the vascular aspects of glaucoma.

METHODS

Three cohorts of individuals over 18 years old were recruited for the study: patients with NTG ($n = 89$), patients with POAG ($n = 102$), and age-matched healthy controls ($n = 59$). This latter group was recruited from the persons accompanying the patients. Glaucoma patients were defined as having characteristic optic disc damage and visual field loss.¹⁹⁻²⁰ For the diagnosis of POAG, an untreated IOP of above 21 mm Hg was required. Current medical treatment, including topical IOP lowering drugs, was continued. The healthy volunteers were screened by a glaucoma specialist (IST) and those with a family history of glaucoma, an increased or asymmetrical cup/disc ratio or any other optic disc structural change (notching, disc hemorrhage), or an IOP

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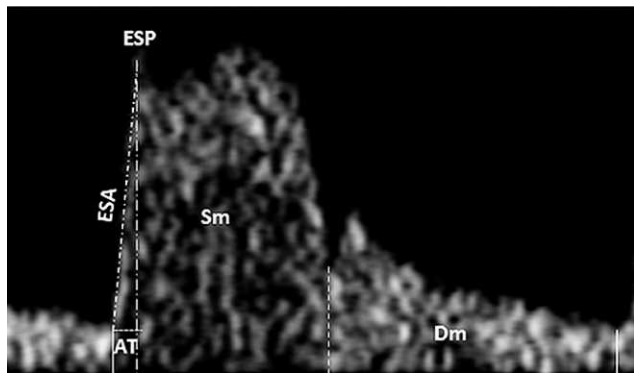


FIGURE 1. OA Doppler wavefront analyzed characteristics. ESA represents the fastest moving portion of the systolic component. ESP corresponds to the acute angle in the wavefront just after the first peak.

above 21 mm Hg were considered as glaucoma suspects and excluded. Patients with a history of ocular trauma or eye disease (except glaucoma) that could not be accounted for by refractive error were excluded.

Measuring Devices

IOP was measured with the Goldmann applanation tonometer (GAT). Central corneal thickness (CCT) was measured using a Pachmate DGH55 (DGH Technology Inc., Exton, PA). Retrobulbar flow velocities and indexes were measured with the Antares CDI device (Siemens, Munich, Germany): PSV, EDV, and RI of the central retina artery (CRA), nasal and temporal short ciliary arteries (NPCA and TPCA, respectively), and ophthalmic artery (OA), as well as Doppler waveform characteristics of this last vessel: ESA, AT, early systolic peak (ESP), and ratio of mean flow velocity during systole and diastole (Sm/Dm) (Fig. 1). Visual acuity was tested using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart placed in the same location at the same distance from the patient under the same illumination for all subjects. Blood pressure measurement was taken from subject's right arm using an electronic sphygmomanometer (Omron, Schaumburg, IL).

Experimental Design

Patients were instructed to avoid caffeine intake, smoking, and exercise for 3 hours prior to the study visit. The study was approved by the ethical review committee (Institutional Review Board) at the University Hospitals Leuven and was conducted in accordance with Good Clinical

Practice within the tenets of the Declaration of Helsinki. Each patient/subject was required to sign an informed consent statement before being enrolled into the study and prior to any study measurements being taken. During the study visit, the following examinations were performed in the same order: visual acuity (using the ETDRS chart placed in the same location at the same distance from the patient under the same illumination for all subjects), IOP measurement by GAT, pachymetry, blood pressure and heart rate measurements, and finally CDI. All CDI measurements were performed by a single observer (LAP) masked to the patient diagnosis. Waveform analysis was performed only in the OA. Only one eye per patient was included in the study. The eye with greater glaucomatous damage was selected in the glaucoma patients, and a randomly selected eye in the healthy individuals.

Statistical Analysis

Kruskal-Wallis tests were used to compare the 3 diagnostic groups on different variables. A Mann-Whitney test was used in pairwise comparisons. Chi-square tests (for 3×2 contingency tables) were used to analyze ESP prevalence. The existence of correlation between variables was explored using Spearman's correlation. Statistical significance was considered when $P < 0.05$. Values depicted as mean \pm SD unless otherwise indicated. Analyses were performed using GraphPad Prism ver. 5.0; (GraphPad Software Inc., La Jolla, CA).

RESULTS

Patient Characteristics

Table 1 summarizes the patient characteristics in the different diagnostic groups with their comparative P values. Kruskal-Wallis test indicated no overall differences in age, visual acuity, central corneal thickness, and mean ocular perfusion pressure (MOPP) (P ranged between 0.26 and 0.88). IOP was statistically different between the 3 groups ($P < 0.001$), with the NTG group presenting lower IOP than the other 2 groups (healthy versus NTG: $P < 0.001$; POAG versus NTG: $P = 0.005$). IOP difference between healthy and POAG groups did not reach statistical significance (healthy versus POAG: $P = 0.12$). While systolic blood pressure was not significantly different between the groups ($P = 0.27$), diastolic pressure was statistically different ($P = 0.02$). Pairwise comparison revealed diastolic pressure in POAG group to be higher than both healthy and NTG groups (versus healthy: $P < 0.01$; versus NTG: $P = 0.03$). Blood pressure amplitudes were lower in both glaucoma groups, but not significantly different between the 2 (healthy versus POAG: $P = 0.02$; healthy versus NTG: $P = 0.03$; NTG versus POAG: $P = 0.89$). A Mann-Whitney test failed to

TABLE 1. Patient Characteristics

	Healthy	NTG	POAG	Kruskal-Wallis/ Mann-Whitney
N	59	89	102	
Age	71.44 \pm 10.0	69.31 \pm 12.1	68.25 \pm 12.6	0.45
IOP	15.07 \pm 2.88	12.99 \pm 2.68	14.61 \pm 4.69	0.0003
Visual acuity	0.22 \pm 0.31	0.30 \pm 0.40	0.24 \pm 0.27	0.27
MD	-	-8.04 \pm 8.97	-9.13 \pm 9.20	0.50
RNFL	-	0.154 \pm 0.10	0.147 \pm 0.09	0.41
CCT	564.2 \pm 33.3	549.8 \pm 34.0	552.8 \pm 38.7	0.26
Systolic BP	152.8 \pm 20.9	146.3 \pm 25.9	149.7 \pm 22.4	0.27
Diastolic BP	82.09 \pm 11.5	82.73 \pm 13.9	86.47 \pm 11.3	0.02
BP amplitude	70.72 \pm 19.0	63.69 \pm 22.4	63.27 \pm 18.1	0.04
MOPP	91.47 \pm 12.1	91.07 \pm 15.1	90.00 \pm 21.9	0.88

Mean values (and SD) are depicted. Kruskal-Wallis indicates P values of overall differences between the diagnostic groups. Mann-Whitney test used in pairwise comparisons.

TABLE 2. Topical Medications

	Healthy	NTG	POAG
Topical			
Beta blockers	-	37 (41.6)	33 (32.4)
Prostaglandin analogs	-	35 (39.3)	36 (35.3)
Carbonic anhydrase inhibitors	-	31 (34.8)	22 (21.6)
α -adrenergic agents	-	7 (7.9)	6 (5.9)

Number of patients and percentage (between brackets) are depicted.

detect any differences in functional or structural damage between the 2 glaucoma groups (visual field mean defect [MD], $P = 0.50$; retinal nerve fiber layer (RNFL) thickness, $P = 0.41$). Topical and systemic medications are summarized in Table 2.

Retrolubar Flow Velocities in Glaucoma Patients and Healthy Controls

Table 3 depicts the data from CDI examinations. Despite a pairwise difference between healthy and NTG patients at the NPCA ($P = 0.04$), the overall comparison between RI from each of the four arteries was not statistically different (P ranged from 0.08 to 0.27). PSV was significantly different in the CRA, NPCA, and TPCA ($P < 0.03$), with pairwise comparison detecting slower velocities in the glaucoma groups when compared with the healthy controls ($P < 0.02$ in all pairwise comparisons). Overall differences in EDV were detected in NPCA ($P = 0.01$), with a Mann-Whitney test detecting NTG patients to have a significantly lower EDV value when compared to the control group ($P < 0.01$), while the POAG group's decrease was only borderline significant ($P = 0.05$). No statistical difference was found in the OA velocities or resistance index (P ranged between 0.08 and 0.96).

Ophthalmic Artery Waveform Analysis in the 3 Diagnostic Groups

Table 4 describes the Doppler waveform characteristics and overall comparison between the 3 groups. The AT, incidence of ESP, and Sm and Dm readings were similar between the groups (P ranged between 0.07 and 0.94). The ESA and the Sm/Dm ratios were significantly different between the groups ($P = 0.03$ and $P = 0.01$, respectively). Pairwise, a Mann-Whitney test detected glaucoma groups to have lower ESA values when compared to healthy controls (versus NTG, $P =$

0.009; versus POAG, $P = 0.04$) as well as smaller Sm/Dm ratios (versus NTG, $P = 0.01$; versus POAG, $P = 0.02$). ESA and Sm/Dm ratio were not different between the two glaucoma groups ($P = 0.65$ and $P = 0.55$, respectively). A Spearman's rank correlation test between the Doppler waveform variables and MOPP detected a statistical relation to exist in the NTG group. In these patients, MOPP correlated positively with ESA ($P = 0.03$; $r = 0.24$) and negatively with AT ($P < 0.01$; $r = -0.37$). No relation existed with Sm, Dm, or Sm/Dm ratio (P ranged between 0.15 and 0.71). In both POAG and healthy control groups, no relation between MOPP and any of the waveform variables was detected (P ranged between 0.15 and 0.98).

Relationship between Ophthalmic Artery Waveform Variables and Blood Pressure Variables

In the healthy group, only blood pressure amplitude had a correlation with one of the waveform variables (Sm/Dm; $P < 0.01$, $r = 0.42$). In the glaucoma groups, on the other hand, there was a positive correlation between the systemic variables and the waveform analysis. The POAG group had both systolic blood pressure and blood pressure amplitude correlating with AT, Sm, and Sm/Dm ($P < 0.05$). In addition to those correlations, in the NTG group there were also associations between waveform variables and MOPP and diastolic blood pressure ($P < 0.05$). The complete analysis is represented in Table 5.

Relationship between Ophthalmic Artery Waveform Variables and Functional and Structural Glaucoma Damage

Table 6 depicts the correlations between the Doppler waveform variables and the degree of functional and structural damage in the glaucoma groups. The Sm/Dm ratio negatively correlated with the extent of glaucomatous damage in both glaucoma groups. In the NTG group, Sm/Dm ratio correlated with structural damage ($P = 0.02$; $r = -0.25$), while in the POAG group this ratio correlated with the functional variable of visual field mean defect ($P = 0.01$; $r = -0.25$). When considering all the glaucoma patients (both POAG and NTG), there is a significant correlation between Sm/Dm ratio and visual field mean defect ($P < 0.001$; $r = -0.26$) with the degree of functional defect correlating with Dm ($P = 0.01$; $r = 0.19$). In these combined glaucoma patient groups, the correlation of Sm/Dm with structural damage did not reach a statistically significant value ($P = 0.07$).

TABLE 3. Comparison of Flow Velocities and Resistance Indexes between Diagnostic Groups

		Healthy	NTG	POAG	Overall	H-N	H-P	N-P
CRA	PSV	12.0 \pm 4.38	10.32 \pm 3.58	10.20 \pm 3.46	0.03	0.02	0.007	0.72
	EDV	3.10 \pm 1.12	2.87 \pm 1.08	2.75 \pm 0.95	0.11	0.12	0.04	0.63
	RI	0.73 \pm 0.07	0.71 \pm 0.08	0.72 \pm 0.07	0.27	0.12	0.35	0.39
NPCA	PSV	11.08 \pm 3.76	8.58 \pm 2.69	9.44 \pm 2.70	<0.001	<0.001	0.005	0.01
	EDV	3.53 \pm 1.53	2.92 \pm 0.99	3.11 \pm 1.08	0.01	0.002	0.05	0.22
	RI	0.68 \pm 0.08	0.65 \pm 0.07	0.66 \pm 0.07	0.12	0.04	0.36	0.21
TPCA	PSV	11.0 \pm 3.87	9.12 \pm 2.81	9.30 \pm 2.60	0.004	0.002	0.006	0.48
	EDV	3.45 \pm 1.36	3.06 \pm 1.09	3.15 \pm 0.92	0.14	0.06	0.31	0.23
	RI	0.68 \pm 0.08	0.66 \pm 0.08	0.66 \pm 0.06	0.27	0.19	0.11	0.92
OA	PSV	40.1 \pm 16.9	33.6 \pm 11.2	35.9 \pm 13.9	0.07	0.02	0.06	0.49
	EDV	7.35 \pm 4.36	6.79 \pm 3.32	7.49 \pm 4.89	0.96	0.75	0.97	0.95
	RI	0.82 \pm 0.07	0.80 \pm 0.07	0.80 \pm 0.07	0.08	0.08	0.05	0.93

Velocities and indexes of the 3 diagnostic groups, at each of the 4 vessels. Pairwise comparisons (H versus NTG, H versus POAG, and NTG versus POAG) were done with a Mann-Whitney test. Overall comparison was done with a Kruskal-Wallis test. Mean values (SD) are depicted. H, healthy.

TABLE 4. Analysis of the Ophthalmic Artery Waveform in the Diagnostic Groups

	Healthy	NTG	POAG	Kruskal-Wallis/ Chi-Square
ESA	688.8 ± 483.6	548.5 ± 337.1	548.1 ± 418.5	0.03
AT	0.049 ± 0.01	0.057 ± 0.05	0.051 ± 0.02	0.59
ESP	3/59	4/89	8/102	0.59
Sm	31.26 ± 14.9	26.08 ± 9.83	27.39 ± 12.1	0.07
Dm	11.57 ± 6.46	10.79 ± 4.77	11.39 ± 6.7	0.94
Sm/Dm ratio	2.94 ± 0.86	2.63 ± 0.84	2.60 ± 0.67	0.01

Mean values (and SD) are depicted. Kruskal-Wallis indicates *P* values of overall differences between the diagnostic groups. Chi-square indicates *P* values of the prevalence of the ESP in each of the diagnostic groups.

DISCUSSION

This study was conducted to evaluate the relevance of studying Doppler waveform variables of the ophthalmic artery in glaucoma patients. Secondly, the authors checked whether correlations could be determined between these variables and parameters of glaucoma damage. Despite the lack of significant differences in velocities and resistance indexes between the ophthalmic arteries of the diagnostic groups, patients in both glaucoma groups had lower ESA and Sm/Dm ratios. Lower Sm/Dm ratios have been suggested to reflect higher levels of systemic arterial compliance.¹⁸ Converting a central pulsatile flow into a steady flow in the peripheral tissues (Windkessel function) depends on the arteries' compliance status. During the cardiac cycle, a portion of the kinetic energy from each systolic pulse is stored within the compliance of the vascular tree by distension of the vessel walls. When intravascular pressure decreases toward the end of systole, this potential energy is released as compliance flow. In low distal resistance settings, this antegrade compliance flow prolongs systole and provides antegrade flow in diastole. When distal resistance is high, the compliance flow is now retrograde and does not contribute to the diastolic pulse.^{21,22} The results of this study would thus reflect a lower distal vascular resistance, an otherwise adaptive response by a vascular territory capable of autoregulation to a state of low-perfusion. In cerebral circulation, for example, decreases in the main arteries' perfusion pressure are compensated by dilation in more distal, pial arteries.^{23,24} This increase in the cross-section vascular area lessens distal resistance and keeps blood flow velocities within normal range.¹² Only when these small vessels reach their maximal dilation capability does mean blood flow velocity (MFV) decay.²⁵ As MFV is part of the vessel's pulsatility index (PI) calculations ($PI = [PSV - EDV]/$

MFV), this leads to a dramatic increase in PI, which has been clinically used as a surrogate of the exhausting of the cerebral circulation autoregulation ability.^{17,26} Beyond such point, there is a linear correlation between pressure and blood flow, as the ability to regulate that flow no longer exists. Considering the existence of a correlation between blood pressure variables and waveform characteristics in glaucoma patients, the authors' data suggests an inability to regulate blood flow in the face of blood pressure changes in these patients. These results are in line with the existing literature on blood flow velocities and arterial pressure in glaucoma patients.^{27,28} In healthy individuals, only blood pressure amplitude had a correlation with a waveform variable (Sm/Dm ratio). In glaucoma patients, however, waveform variables were much more sensitive to changes in blood pressure, especially in the NTG population. While the results of this study in healthy individuals are in line with published literature where blood pressure amplitude affects OA blood flow,^{29,30} the fact that the glaucoma patients in this study had a different hemodynamic profile may be responsible for the different waveform patterns. The higher diastolic blood pressure values and consequently decrease in blood pressure amplitude could be associated with an overall increase in peripheral vascular tonus and relaxation impairment.

Interestingly, the authors identified a correlation to exist between the extent of glaucomatous damage and a shift to the left in blood flow, mainly at the expense of a decrease of the diastolic mean flow (Fig. 2). As these results reveal glaucoma patients to have simultaneous signs of changes in blood flow patterns and inadequate mechanisms of autoregulation despite similar MOPP values when compared to the healthy groups, none of the previous hypotheses would provide a full explanation. A possible alternative is presented by Doppler studies elsewhere in the body. Transmittal flow analysis for

TABLE 5. Correlation between OA Waveform Characteristics and Cardiovascular Parameters

		ESA	AT	Sm	Dm	Sm/Dm Ratio
Healthy	BP sys	0.21	0.06	0.42	0.93	0.08
	BP dias	0.43	0.55	0.73	0.68	0.17
	BP amp	0.07	0.08	0.39	0.52	<0.01 (0.42)
	MOPP	0.33	0.90	0.52	0.58	0.77
POAG	BP sys	0.09	0.03 (-0.23)	0.03 (0.24)	0.97	0.01 (0.27)
	BP dias	0.97	0.24	0.26	0.46	0.53
	BP amp	0.02 (0.24)	0.02 (-0.25)	0.02 (0.24)	0.74	<0.01 (0.38)
	MOPP	0.88	0.15	0.19	0.98	0.34
NTG	BP sys	<0.01 (0.32)	<0.01 (-0.36)	0.02 (0.25)	0.12	0.31
	BP dias	0.57	0.049 (-0.22)	0.46	0.05 (0.22)	0.06
	BP amp	<0.01 (0.44)	<0.01 (-0.35)	<0.01 (0.31)	0.24	0.02 (0.25)
	MOPP	0.03 (0.24)	<0.01 (-0.37)	0.15	0.19	0.71

P values of Spearman correlations are depicted (values on coefficient of correlation in brackets when *P* < 0.05). BP sys, systolic blood pressure; BP dias, diastolic blood pressure; BPA, blood pressure amplitude (BP systolic - BP diastolic).

TABLE 6. Correlation between OA Waveform and Structural/Functional Glaucoma Damage

	NTG		POAG		NTG + POAG	
	MD	RNFL	MD	RNFL	MD	RNFL
ESA	0.58	0.69	0.70	0.86	0.95	0.74
AT	0.48	0.62	0.16	0.34	0.14	0.34
Sm	0.59	0.57	0.69	0.7	0.34	0.85
Dm	0.25	0.08	0.10	0.93	0.01 (0.19)	0.25
Sm/Dm ratio	0.08	0.02 (−0.25)	0.01 (−0.25)	0.73	<0.001 (−0.26)	0.07

P values of Spearman correlations are depicted (values on coefficient of correlation in brackets when *P* < 0.05).

ventricular diastolic dysfunction has remarkable similarities to the data found in this study. A normal relaxed ventricle has a left upward waveform. A stiffer, less compliant ventricle prolongs relaxation time, reducing early velocities and increasing late diastolic velocities, producing a rightward movement. However, when the ventricular dysfunction is high enough, there is a “pseudo-normalization” of the waveform. The very high ventricular stiffness, coupled with a secondary upstream increase in pressure, returns the blood flow pattern into an otherwise normal left upward waveform. In the last stages of diastolic dysfunction, a restrictive pattern develops where flow is almost abolished in this last part of the cardiac cycle.^{31,32} This waveform progression pattern is very interesting, as the more advanced glaucoma waveform's shift to the left could be compared to this pseudo-normalization phenomenon. While the ocular circulation and its similarities to other territories remains incompletely understood, more studies would be needed to validate this diastolic dysfunction. This dysfunction could, however, be associated to a number of conditions known to exist in glaucoma patients, from vascular endothelial dysfunction³³ to increases in the levels of vasoconstrictive agents such as endothelin-1.³⁴ Additionally, there are additional factors that may potentiate the vascular changes that may exist in these patients. The curved anatomy of the OA makes it more vulnerable to changes in tone and its possible repercussion on perfusion pressures. Large, more muscular straightline arteries, such as the carotid arteries, require up to 70% of their lumen to be obstructed in order to have a clinically significant hemodynamic impact. However, a change of just 36% in the luminal diameter of a curved arterial segment, such as the OA, would be enough to cause a decrease in the perfusion pressure.³⁵ While changes of this magnitude are still unlikely, further studies are needed to assess the in vivo diameter of this vessel throughout its entire path.

Of note, the current hypothesis of impairment in the compliance status of the ocular circulation may be important when assessing vascular resistance through Doppler studies. As changes in compliance and blood pressure amplitude has

been suggested to affect the ability of RI to reflect true vascular resistance,³⁶ this impairment in compliance could potentially affect the interpretation of this widely-used CDI variable.

There are, however, important limitations in this study. The authors' Doppler studies have not included the analysis of the carotid arteries that could detect any increased prevalence of significant stenosis in the glaucoma groups. Existing literature, however, does not support this idea.^{37,38} Secondly, the authors could not determine the perfusion pressure in the ophthalmic artery. The authors' interpretation of the waveform is, however, supported in existing data from Doppler studies in other vascular territories in both physiological and pathological conditions. Until the mechanisms of ocular vascular dysfunction are fully understood, our interpretation of these results remains a working hypothesis. Furthermore, the fact that a significant number of patients from both glaucoma groups were under treatment with vasoactive agents, such as topical carbonic anhydrase inhibitors, could have introduced an additional bias that must be taken into account when concluding about the patients' ocular circulation. Finally, while the waveform analyses of the other retrobulbar arteries would have been interesting to perform, the lack of a clear visible dicrotic notch in some of those arteries' waveforms (such as NPCA and TPCA) would have increased any existing bias in differentiating the ejected from the reflected wave components (systolic and diastolic components, respectively).

In conclusion, the authors' data suggest that these Doppler waveform analyses could add an extra value to ocular blood flow studies. A shift to the right in the ophthalmic artery waveform is identifiable even in the absence of differences in peak systolic or end-diastolic blood flow velocities. While the nature of this pattern change is not completely understood, further studies are still needed in order to better understand what may cause such shift changes, thus providing a better understanding of the possible underlying vascular dysfunction.

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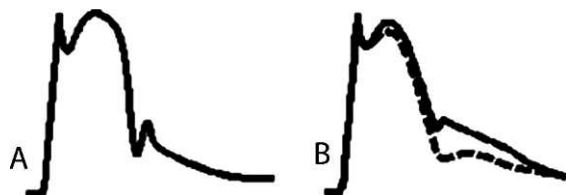


FIGURE 2. Examples of ophthalmic artery waveforms in healthy controls (A) and glaucoma patients (B). In B, despite non-significant changes in peak systolic and end-diastolic velocities, there is a shift in blood velocities toward the end of the cardiac cycle when compared to the healthy controls (solid). More extensive glaucoma damage would correlate with a decrease in the latter, diastolic component of the cardiac cycle, and thus an increase in mean systolic/diastolic velocity ratios (dashed).

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