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Ocular pulse amplitude and Doppler waveform analysis in glaucoma patients

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ABSTRACT.

Purpose: **To determine the correlation between ocular blood flow velocities and ocular pulse amplitude (OPA) in glaucoma patients using colour Doppler imaging (CDI) waveform analysis.**

Method: **A prospective, observer-masked, case-control study was performed. OPA and blood flow variables from central retinal artery and vein (CRA, CRV), nasal and temporal short posterior ciliary arteries (NPCA, TPCA) and ophthalmic artery (OA) were obtained through dynamic contour tonometry and CDI, respectively. Univariate and multiple regression analyses were performed to explore the correlations between OPA and retrobulbar CDI waveform and systemic cardiovascular parameters (blood pressure, blood pressure amplitude, mean ocular perfusion pressure and peripheral pulse).**

Results: **One hundred and ninety-two patients were included [healthy controls: 55; primary open-angle glaucoma (POAG): 74; normal-tension glaucoma (NTG): 63]. OPA was statistically different between groups (Healthy: 3.17 ± 1.2 mmHg; NTG: 2.58 ± 1.2 mmHg; POAG: 2.60 ± 1.1 mmHg; $p < 0.01$), but not between the glaucoma groups ($p = 0.60$). Multiple regression models to explain OPA variance were made for each cohort (healthy: $p < 0.001$, $r = 0.605$; NTG: $p = 0.003$, $r = 0.372$; POAG: $p < 0.001$, $r = 0.412$). OPA was independently associated with retrobulbar CDI parameters in the healthy subjects and POAG patients (healthy CRV resistance index: $\beta = 3.37$, CI: 0.16–6.59; healthy NPCA mean systolic/diastolic velocity ratio: $\beta = 1.34$, CI: 0.52–2.15; POAG TPCA mean systolic velocity: $\beta = 0.14$, CI 0.05–0.23). OPA in the NTG group was associated with diastolic blood pressure and pulse rate ($\beta = -0.04$, CI: −0.06 to −0.01; $\beta = -0.04$, CI: −0.06 to −0.001, respectively).**

Conclusions: **Vascular-related models provide a better explanation to OPA variance in healthy individuals than in glaucoma patients. The variables that influence OPA seem to be different in healthy, POAG and NTG patients.**

Key words: colour Doppler imaging – normal-tension glaucoma – ocular pulse amplitude – primary open-angle glaucoma – vascular dysregulation

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Introduction

Glaucoma is one of the leading causes of irreversible blindness in the developed world (Kingman 2004). Extensive research is continuously being carried out both to improve treatment strategies and to uncover the underlying disease mechanisms. A number of studies have consistently demonstrated patients with primary open-angle glaucoma (POAG) and particularly the ones with normal-tension glaucoma (NTG), to have systemic signs of vascular dysfunction. These patients are more prone to have lower ocular perfusion pressures, peripheral vasospasms, migraine, low retrobulbar flow velocities and decreased ocular pulse amplitudes (OPA; Wang et al. 1997; Broadway & Drance 1998; Stalmans et al. 2008; Leske 2009).

This latter variable (OPA) represents the amplitude between the systolic and diastolic intraocular pressure (IOP) during a cardiac cycle and is measured at the corneal level by a dynamic contour tonometer (DCT). It has been suggested that these IOP fluctuations reflect a change in the choroidal blood volume (Langham et al. 1989), a tissue which is supplied by the short posterior ciliary arteries. Its clinical relevance has been consistently documented. Indeed, lower OPA is associated with advanced stages of the disease, and has been linked to more progressive forms of glaucoma (Vulsteke et al. 2008; Kac et al. 2011; Kynigopoulos et al. 2012). While these lower OPA readings could be

related to a decrease in choroidal flow suggested to exist in glaucoma patients (Marangoni et al. 2012; Samra et al. 2013), the mechanisms behind these lower pulse amplitudes remain unclear. A previous ocular blood flow study using colour Doppler imaging (CDI) has suggested that OPA reflects vascular resistance of retrobulbar vessels in healthy individuals, but not in glaucoma patients (Stalmans et al. 2009). That study, however, assessed vascular resistance (RI) as a ratio calculated by only two velocity points (peak systolic and end-diastolic velocities) out of the entire Doppler waveform pattern. Furthermore, as this variable has been suggested to have a nonlinear correlation with the blood velocity distribution throughout the cardiac cycle, the information potentially obtained by this variable is limited (Abegão Pinto et al. 2012c). Recently, it has been suggested that more complete Doppler waveform analysis of the retrobulbar vessels (including early systolic acceleration, mean systolic and diastolic flow velocities and the ratio between those two) might provide valuable information concerning the arteries' elasticity and compliance and their ability to buffer and accommodate a pulsatile blood flow (Abegão Pinto et al. 2012a).

Our purpose with this study was therefore to determine whether OPA, as assessed by DCT, correlates with these novel retrobulbar blood-flow-related variables. Additionally, we explored whether these associations could provide further insights into the nature of OPA in the glaucoma population.

Methods

Subjects groups

Three cohorts of individuals over 18 years old were recruited for the study: patients with NTG ($n = 63$), patients with POAG ($n = 74$) and age-matched healthy controls ($n = 55$). This latter group was recruited from the persons accompanying the patients (while excluding blood relatives). Glaucoma patients were defined as having characteristic optic disc damage and visual field loss (Jampel 1997). For the diagnosis of POAG, an untreated IOP of above 21 mmHg or patients with a formal diagnosis of POAG and treated with IOP reducing agents was required. No criteria for the severity of glaucoma existed other than the ability to perform a reliable visual field test. Current medical treatment, including topical IOP-lowering drugs, was continued. The healthy volunteers were screened by a glaucoma specialist (IS) and those with a family history of glaucoma, an increased or asymmetrical cup/disc ratio or any other optic disc structural change (notching, disc haemorrhage), or an IOP above 21 mmHg were considered as glaucoma suspects and excluded. Subjects in all cohorts with a history of ocular trauma or eye disease (including high ametropias, defined as hyperopia >4Dp and myopia >6Dp) were excluded. Diabetic patients and all forms of secondary glaucomas (including pseudo-exfoliative) were also excluded from the study.

Measuring devices

Intraocular pressure was measured with Goldmann applanation tonometer (GAT) and dynamic contour tonometry (DCT – Pascal®, Ziemer Ophthalmic System AG, Port, Switzerland), with OPA being recorded from this latter tonometry reading. OPA readings were repeated twice, and the average between two measurements was considered. Only quality readings of 2 or less were considered. Central corneal thickness (CCT) was measured using a Pachmate DGH55 (DGH Technology Inc., Exton, PA, USA). Retrobulbar Doppler waveforms of the central retinal vessels (artery and vein, CRA and CRV, respectively), short posterior ciliary arteries (nasal and temporal, NPCA and TPCA, respectively) and ophthalmic artery (OA) were obtained with the Antares CDI device (Siemens, Munich, Germany). To increase the visibility of the dicrotic notch in each artery, the pulse repetition frequency was adjusted so as to maximize the dimensions of waveform. 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, USA).

Experimental design

In this prospective, observer-masked, case-control study, patients were instructed to avoid caffeine intake, smoking, and exercise for 3 hr 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, IOP measurement by GAT and DCT, pachymetry, blood pressure and peripheral pulse rate measurements and finally CDI. All CDI measurements were performed according to the published consensus methodology (Stalmans et al. 2011) by a single observer (LAP) masked to the patient diagnosis. An offline analysis of the waveform analysis was performed in all the retrobulbar arteries (CRA, NPCA, TPCA and OA) by the same observer to determine the following variables (Fig. 1): acceleration (Acc), systolic and diastolic mean velocities (S_m and D_m) and their ratio (S_m/D_m), peak systolic and end-diastolic velocity (PSV and EDV), resistance index (RI) and mean flow velocities (MFV) as described elsewhere (Abegão Pinto et al. 2012a). The following variables were analysed in the central retinal vein: maximal and minimal velocity (V_{max} and V_{min}, respectively) and RI (Fig. 1). 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.

This study has been registered in the clinicaltrial.gov (NCT01840202).

Statistical methodology

Normality tests (D'Agostino & Pearson omnibus) were performed, with nonlinear regression models (Gaussian curves) designed to characterize OPA distribution in each cohort. Kruskal–Wallis with Dunn's correction for pairwise comparison tests were used to

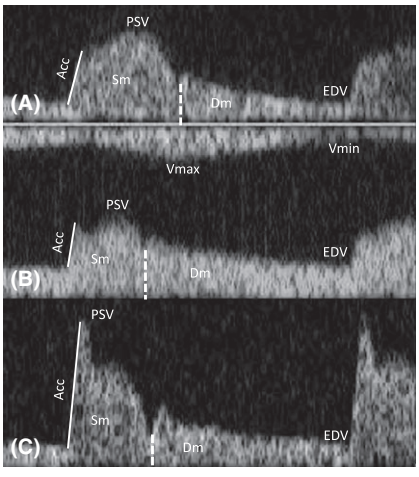

Fig. 1. Doppler waveform of the central retinal artery and vein (A), the short ciliary arteries, both nasal and temporal (B) and the ophthalmic artery (C). Acc represents the fastest moving portion of the systolic component; PSV, the peak systolic velocity; EDV, the end-diastolic velocity; and S_m and D_m, the mean systolic and diastolic velocity, respectively.

compare the means between the three diagnostic groups. The existence of correlation between variables was explored using Spearman's correlation. Multiple regression analyses were performed to identify independent associations to OPA. Statistical significance was considered when two-sided p value < 0.05. Values depicted as mean ± SD unless otherwise indicated.

Results

Patient characteristics

Table 1 summarizes the patient characteristics in the different cohorts with their comparative p values. No differences were observed in age, visual acuity, central corneal thickness, blood pressure variables (systolic, diastolic, amplitude and mean ocular perfusion pressures) and peripheral pulse (p range between 0.08 and 0.85). IOP was significantly different (p = 0.02), with lower values in the NTG group when compared to both healthy and POAG groups (versus healthy p = 0.03; versus POAG p < 0.01), but no difference in IOP between these two latter groups (p = 0.70).

Ocular pulse amplitude was statistically different between the cohorts (healthy: 3.17 ± 1.2 mmHg; NTG: 2.58 ± 1.2 mmHg; POAG: 2.60 ± 1.1 mmHg; p < 0.01). Both glaucoma groups had lower OPA when compared to the healthy cohort (versus NTG p = <0.01; versus POAG p < 0.01), but no difference was detected between the NTG and POAG groups (p = 0.60). Figure 2 illustrates the frequency distribution (and the corresponding Gaussian curves) of OPA in the three cohorts.

Table 1. Patients characteristics.

	Healthy	NTG	POAG	Kruskal–Wallis
N	55	63	74	
Age (years)	65.1 ± 11.0	69.7 ± 9.0	67.4 ± 10.7	0.08
IOP (mmHg)	17.1 ± 3.3	15.6 ± 2.8	17.5 ± 4.2	0.02
Visual acuity (logMar)	0.14 ± 0.2	0.17 ± 0.3	0.10 ± 0.2	0.37
MD (dB)	–	−9.8 ± 8.6	−10.9 ± 8.9	0.49
CCT (μm)	557 ± 39.6	541 ± 42.2	548 ± 37.1	0.34
Systolic BP (mmHg)	150.0 ± 19.4	150.3 ± 24.9	152.1 ± 20.2	0.59
Diastolic BP (mmHg)	82.8 ± 11.9	83.7 ± 12.2	86.0 ± 11.8	0.22
BP amplitude (mmHg)	66.6 ± 16.8	66.6 ± 22.9	66.1 ± 16.9	0.85
MOPP (mmHg)	53.5 ± 9.6	55.9 ± 10.3	54.4 ± 9.8	0.40
Pulse (bpm)	69.3 ± 9.8	63.4 ± 12.8	69.9 ± 12.6	0.10

Mean values (and SD) are depicted. Kruskal–Wallis indicates p values of overall differences between the diagnostic groups. IOP indicates intraocular pressure; MD, mean defect; CCT, central corneal thickness; BP, blood pressure; and MOPP, mean ocular perfusion pressure [(2/3 diastolic+1/3 systolic BPs)*2/3-Goldmann tonometry].

Retrobulbar Doppler waveform analysis

Table 2 depicts the retrobulbar Doppler waveform variables for each cohort. Flow velocities in the CRA, CRV, TPCA and OA were reduced in both glaucoma groups when compared to healthy individuals (p < 0.05). Of the entire Doppler parameters, only the CRA's EDV (p = 0.01) and each of the venous flow parameters (p < 0.04 in all comparisons) were statistically different between the two glaucoma cohorts.

Relationship between OPA and Ocular and Systemic vascular parameters

Table 3 illustrates the univariate statistically significant associations between ocular and systemic parameters and OPA. The Doppler-related variables that did not have a statistical correlation with OPA in any of the three groups were not represented.

Multiple regression analysis models were constructed for each of the cohorts, using OPA as the dependent parameter and all those parameters that were significantly associated with

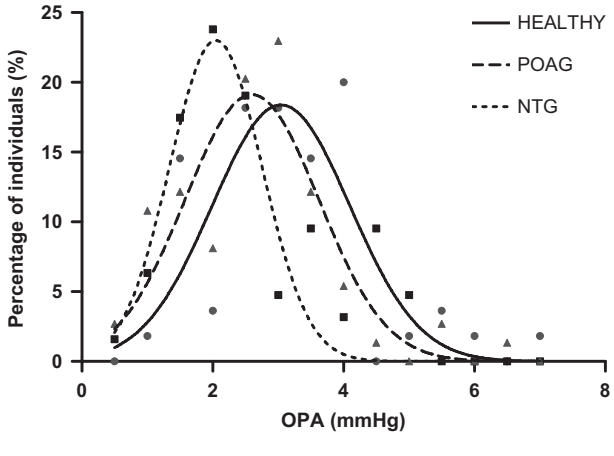

Fig. 2. Frequency distribution of OPA in the three experimental groups (in percentage). Despite similar absolute means with the primary open-angle glaucoma (POAG) group, the Gaussian distribution of NTG shows a smaller, left-oriented OPA curve. Considering 0.5 mmHg intervals, the median OPA in NTG was 2.0 mmHg (23.8%) while in POAG and healthy groups was 3.0 mmHg (23.0%) and 4.0 mmHg (20%), respectively. Data points refer to healthy (circles), POAG (triangles) and NTG (squares).

Table 2. Comparison of Doppler waveform variables between diagnostic groups.

	Healthy (n = 55)	NTG (n = 63)	POAG (n = 74)	Overall	NTG versus POAG
CRA					
Acc	160 ± 66	127 ± 57	127 ± 66	<0.002	0.27
PSV	12.9 ± 4.4	10.6 ± 3.5	9.63 ± 3.6	<0.001	0.07
EDV	3.55 ± 1.3	2.88 ± 0.9	2.63 ± 0.8	<0.001	0.01
MFV	6.88 ± 2.5	5.55 ± 1.8	5.16 ± 2.0	<0.001	0.11
RI	0.72 ± 0.1	0.71 ± 0.1	0.71 ± 0.1	0.88	0.87
S_m	11.0 ± 4.1	8.85 ± 3.1	8.14 ± 3.1	<0.001	0.12
D_m	4.99 ± 1.9	3.85 ± 1.3	3.64 ± 1.3	<0.001	0.22
S_m/D_m	2.27 ± 0.5	2.33 ± 0.5	2.27 ± 0.5	0.52	0.43
CRV					
V_{max}	5.97 ± 1.7	5.19 ± 1.4	4.51 ± 1.3	<0.001	<0.001
V_{min}	3.45 ± 0.9	3.02 ± 0.6	2.84 ± 0.7	<0.001	0.04
RI	0.41 ± 0.1	0.39 ± 0.1	0.35 ± 0.1	<0.004	0.03
NPCA					
Acc	128 ± 49	103 ± 40	112 ± 52	0.03	0.63
PSV	10.8 ± 4.1	9.52 ± 3.0	9.17 ± 2.8	0.08	0.58
EDV	3.81 ± 1.7	3.33 ± 1.2	3.00 ± 0.9	0.02	0.10
MFV	6.39 ± 2.9	5.61 ± 1.9	5.29 ± 1.6	0.14	0.42
RI	0.65 ± 0.1	0.64 ± 0.1	0.66 ± 0.1	0.24	0.13
S_m	8.84 ± 3.1	8.08 ± 2.7	7.67 ± 2.4	0.11	0.40
D_m	4.72 ± 2.0	4.27 ± 1.6	3.96 ± 1.3	0.12	0.30
S_m/D_m	1.97 ± 0.4	1.94 ± 0.3	1.96 ± 0.3	0.58	0.56
TPCA					
Acc	128 ± 58	115 ± 49	127 ± 47	0.22	0.11
PSV	11.1 ± 3.7	9.54 ± 3.3	9.80 ± 2.9	0.01	0.30
EDV	3.80 ± 1.4	3.22 ± 1.2	3.19 ± 1.1	<0.006	0.70
MFV	6.74 ± 2.3	5.62 ± 2.2	5.65 ± 1.8	<0.003	0.44
RI	0.65 ± 0.1	0.66 ± 0.1	0.67 ± 0.1	0.16	0.24
S_m	9.49 ± 2.8	8.13 ± 2.8	8.39 ± 2.5	<0.005	0.28
D_m	5.11 ± 1.7	4.14 ± 1.6	4.30 ± 1.6	<0.002	0.44
S_m/D_m	1.91 ± 0.4	2.01 ± 0.3	2.02 ± 0.4	0.04	0.80
OA					
Acc	599 ± 310	492 ± 233	462 ± 173	0.02	0.58
PSV	39.7 ± 17	32.9 ± 10	31.2 ± 10	<0.002	0.20
EDV	7.96 ± 4.6	6.03 ± 3.8	5.96 ± 3.1	<0.007	0.83
MFV	18.0 ± 8.5	14.8 ± 6.4	14.2 ± 5.9	0.01	0.73
RI	0.80 ± 0.1	0.82 ± 0.1	0.81 ± 0.1	0.25	0.27
S_m	30.2 ± 14	25.9 ± 8.9	24.7 ± 8.6	0.03	0.44
D_m	11.9 ± 6.6	9.45 ± 5.2	9.10 ± 4.5	<0.007	0.91
S_m/D_m	2.79 ± 1.1	3.13 ± 1.2	3.07 ± 1.2	0.15	0.54

Kruskal–Wallis test with Dunn's correction was used in the overall and pairwise comparison between cohorts. NTG indicates normal-tension glaucoma; POAG, primary open-angle glaucoma; CRA, central retinal artery; CRV, central retinal vein; NPCA, nasal posterior ciliary arteries; TPCA, temporal posterior ciliary arteries; OA, ophthalmic artery; Acc, acceleration speed (cm/seg^2); PSV, peak systolic velocity (cm/seg); EDV, end-diastolic velocity (cm/seg); MFV, mean flow velocity (cm/seg); S_m, mean systolic velocity (cm/seg); D_m, mean diastolic velocity (cm/seg); V_{max}, maximal venous velocity (cm/seg); V_{min}, minimal venous velocity (cm/seg); and RI, resistivity index.

OPA in univariate analysis as independent variables. Multicollinearity in each model was corrected until the highest possible model fit was achieved.

All three models were statistically significant in explaining OPA variance, with a higher degree of correlation in the healthy group than in either of the glaucoma cohorts (healthy $p < 0.001$, $r = 0.605$; NTG $p = 0.003$, $r = 0.372$; POAG $p < 0.001$, $r = 0.412$; Table 4). The difference in coefficient correlations between the healthy and the glaucoma models was borderline significant (one-sided P Fisher r-to-z transformation: healthy versus POAG: $p = 0.07$; healthy versus NTG: $p = 0.05$). The independent variables were different for each group. While OPA in the healthy and POAG groups was independently associated with retrobulbar flow variables (healthy: CRV RI: $\beta = 3.37$, CI: 0.16–6.59; NPCA S_m/D_m: $\beta = 1.34$, CI: 0.52–2.15; POAG: IOP $\beta = 0.13$, CI 0.07–0.20, TPCA S_m $\beta = 0.14$, CI 0.05–0.23; respectively), OPA in the NTG group was rather associated with systemic variables such as diastolic blood pressure and pulse rate ($\beta = -0.04$, CI:−0.06 to −0.01; $\beta = -0.04$, CI: −0.06 to −0.001; respectively).

Discussion

The current study showed that the parameters obtained from a detailed Doppler waveform analysis significantly associated with OPA. In fact, once the entire Doppler waveform spectrum was taken into account, none of the classic CDI-studied variables (such as PSV, EDV or arterial RI) were independently associated with OPA. Accordingly, analysing time-continuous variables such as systolic or diastolic mean flows may better explain OPA fluctuations than a classic two-point assessment of the retrobulbar haemodynamics.

The strength of correlation of our constructed vascular-orientated models differs between healthy and glaucoma groups, with a weaker correlation between OPA and the ocular and systemic vascular parameters in both POAG and NTG. This would suggest that in glaucoma patients, other non-vascular variables may be important determinants of OPA. These variables could relate to differences in ocular elasticity and compliance between glaucoma patients and healthy individuals as suggested by several authors (Sigal et al. 2005; Hommer et al. 2008; Dastiridou et al. 2013; Wang et al. 2013). For instance, any determined increase in intraocular blood volume would lead to a smaller increase in pressure if the overall compartment is elastic rather than rigid. Accordingly, the lower readings in OPA by an external tonometer (such as the DCT) found in glaucoma patients could be related to the mechanical properties of the ocular compartment walls (for instance, a more elastic sclera). Furthermore, from a structural point of view, for the choroidal-related pressure pulse to reach the cornea, it must go through a number of tissues. Accordingly, these structural properties of all those tissues (vitreous, lens, iris, aqueous humour and the cornea) could buffer that wave pulse. Our results would thus suggest that the summation of the input from all these structures in generating OPA are more relevant in glaucoma patients

Table 3. Univariate correlations with OPA in the three cohorts.

	Healthy (r)	POAG (r)	NTG (r)
Age	–	–	–
CCT	–	–	–
IOP	0.28	0.56	–
CRA – Acc	0.30	–	–
CRA – S_m/D_m	0.32	0.34	0.47
CRA – RI	–	0.31	0.37
CRV – V_{max}	–	–	0.28
CRV – RI	0.32	–	0.41
NPCA – S_m/D_m	0.41	–	0.33
NPCA – RI	0.30	–	–
TPCA – Acc	–	0.27	–
TPCA – PSV	–	0.28	–
TPCA – S_m	–	0.27	–
TPCA – S_m/D_m	0.35	0.24	–
TPCA – RI	0.31	0.30	–
OA – PSV	0.26	–	–
OA – S_m	–	0.31	–
OA – MFV	–	0.27	–
OA – S_m/D_m	0.19	−0.01	–
MOPP	–	–	−0.29
Systolic BP	–	–	–
Diastolic BP	–	–	−0.44
BP Amp	0.40	–	0.36
Pulse	–	–	−0.53

r values depicted if $p < 0.05$. The remaining Doppler-related variables that are not represented did not have a statistical correlation with OPA. POAG indicates primary open-angle glaucoma; NTG, normal-tension glaucoma; CCT, central corneal thickness; IOP, intraocular pressure; CRA, central retinal artery; NPCA, nasal posterior ciliary artery; TPCA, temporal posterior ciliary artery; OA, ophthalmic artery; MOPP, mean ocular perfusion pressure [(2/3 diastolic+1/3 systolic BPs)*2/3-Goldmann tonometry]; BP, blood pressure; BP Amp, blood pressure amplitude (BP systolic – BP diastolic);Acc, acceleration speed; PSV, peak systolic velocity; MFV, mean flow velocity; S_m, mean systolic velocity; D_m, mean diastolic velocity; V_{max}, maximal venous velocity; and RI, resistivity index.

Table 4. Multiple regression models and its independent-related variables for each of the cohorts.

	Variable	p value	β coefficient	Confidence interval
Healthy ($r = 0.61$, $p < 0.001$)	CRV RI	0.04	3.37	0.16 to 6.59
	NPCA S_m/D_m	0.002	1.34	0.52 to 2.15
POAG ($r = 0.41$, $p < 0.001$)	IOP	<0.001	0.13	0.07 to 0.20
	TPCA S_m	0.003	0.14	0.05 to 0.23
NTG ($r = 0.37$, $p = 0.003$)	Diastolic BP	0.007	−0.04	−0.06 to −0.01
	Pulse	0.04	−0.04	−0.06 to −0.001

Data representing the following linear models: Healthy = −2.531 + 0.06782*IOP + 0.002841 *CRA Acc − 0.7433*CRA S_m/D_m + 3.374*CRV RI + 1.335*NPCA S_m/D_m + 1.978*TPCA RI + 0.02307*OA MFV + 0.002581*BP amp; POAG = −3.313 + 0.1329*IOP + 0.2456*CRA S_m/D_m+ 3.599*CRA RI − 0.001070*TPCA Acc + 0.1383*TPCA S_m − 0.4831*TPCA S_m/D_m + 0.02498*OA S_m − 0.01092*OA MFV; NTG = 8.019 + 0.3371*CRA S_m/D_m − 2.621*CRA RI − 0.1074*CRV V_{max} + 2.553*CRV RI + 0.06040*NPCA S_m/D_m − 0.03584*Diastolic BP − 0.03068*Pulse.

than in healthy individuals (as the vascular models – while significant – explain a smaller degree of OPA variance than in healthy controls). Recent advances in optical coherent tomography (OCT) technology, which allow *in vivo* mapping of the scleral thickness, may provide further insight into this discussion (Park et al. 2012). More studies will be needed to determine whether the differences in the correlation of OPA and ocular-related variables between healthy and glaucoma patients might be related to such structural differences.

Interestingly, our results also suggest that under physiological conditions (i.e. healthy eyes), the RI of the CRV would be involved in OPA. While it would be intuitive that a relation should exist between the arterial blood input and venous output, the retinal circulation is only responsible for a small portion of the overall blood volume. However, as the CRV is a low pressure system, the fluctuations in pressure inside the eye (OPA) may directly influence venous output (Donnelly & Subramanian 2009; Abegão Pinto et al. 2012b). Both POAG and NTG patients are thought to have a higher-than-expected intraluminal venous pressure (Morgan et al. 2004). Therefore, this compression caused by the pulsatile choroidal flow would be unlikely to impact the retinal venous output in glaucoma patients, which may explain why the association between OPA and CRV RI was not present in these patient groups.

In NTG patients, there are no direct associations between local ocular-related factors and OPA. Even the independent statistically associated variables have a low correlation coefficient on the overall OPA detection. However, the fact that blood pressure and heart rate parameters can significantly influence OPA would imply that the local vascular auto-regulation is no longer able to compensate for these changes. Indeed, within the limits of our study population, in healthy and even POAG patients, the ocular blood flow appears to be able to buffer the influence of the systemic cardiovascular parameters. This is in line with a number of studies on ocular blood flow in glaucoma patients, where NTG patients show signs of abnormal vascular regulation ability (Gherghel et al. 2000; Galassi et al. 2011).

Our study has limitations. Systemic antihypertensive medication was not withheld for this study, which may have introduced a confounding factor in all three groups. On ethical grounds, it was deemed excessive to withdraw important medication in a study where no direct benefit could come to the patient. For this reason, this is a common limitation of observational studies in elderly patients (where a number of comorbidities are likely to exist). Secondly, as illustrated in Fig. 2, the Gaussian curve in NTG shows a smaller range in OPA values. While expected, it is therefore not unusual that smaller correlation coefficients with other variables were detected in this narrow frequency distribution. Further studies involving

analysis of non-vascular-related variables may help further explain this smaller OPA variance in glaucoma patients. For instance, by combining other ocular blood flow technologies that enable the accurate calculation of volume change (such as the Langham ocular blood flow system, laser interferometry or subfoveal laser Doppler flowmetry), information on differences in ocular rigidity can be added to the current CDI-based analysis.

In conclusion, our study aimed at exploring whether an association between the blood volume change necessary to produce a pulse pressure inside the eye and the blood velocity in the arteries that nurture the eye existed. The answers to this – as the results from the current study suggests – could vary between healthy and glaucoma groups, thus implying OPA readings could represent a balance in the forces involved that may vary according to each patient (healthy, NTG or POAG). Nevertheless, our results seem to suggest that OPA variance is more strongly influenced by vascular-related factors in healthy individuals than in glaucoma patients. The smaller OPA values in glaucoma patients may therefore relate to differences in non-vascular variables.

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