# Ocular Blood Flow and Systemic Blood Pressure in Patients with Primary Open-Angle Glaucoma and Ocular Hypertension

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**Purpose.** There is evidence that altered optic nerve head (ONH) blood flow may play a role in the development and progression of glaucoma. In the present study, the baseline characteristics were examined in a study population participating in a clinical trial in which the ocular hemodynamic effects of timolol and dorzolamide were compared.

**Methods.** One hundred forty patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) were included in this trial and their baseline parameters compared with those of a group of 102 age-matched control subjects. Scanning laser Doppler flowmetry was used to measure blood flow in the temporal neuroretinal rim and the cup of the ONH. Pulsatile choroidal blood flow was assessed by laser interferometric measurement of fundus pulsation amplitude. In addition, hemodynamic parameters and mean arterial pressure were calculated in both groups.

**Results.** All ocular hemodynamic parameters were significantly lower in the POAG/OHT group compared with the healthy control group ($P < 0.001$ each). In addition, a significant positive correlation between laser Doppler flowmetry readings and mean arterial pressure was observed in patients with glaucoma but not in healthy control subjects. Likewise, the correlation coefficient between fundus pulsation amplitude and mean arterial pressure was higher in patients with glaucoma than in healthy control subjects.

**Conclusions.** The present study indicates reduced ONH and choroidal blood flow and an abnormal association between blood pressure and ocular perfusion in patients with primary open-angle glaucoma or ocular hypertension, independent of topical antiglaucoma medication. Hence, vascular dysregulation appears to be an early manifestation in glaucoma that is not caused by pharmacologic intervention. (*Invest Ophthalmol Vis Sci.* 2004;45:834–839) DOI:10.1167/iovs.03-0461

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There is increasing evidence that ocular blood flow abnormalities are involved in the pathogenesis of glaucoma.[1] Hence, there is considerable interest in potential ocular hemodynamic effects of currently available antiglaucoma drugs. A large number of clinical studies have been performed to clarify this issue by using different techniques for the assessment of ocular blood flow, and these studies have yielded partially contradictory results.[2] However, all previously published studies are limited by the small number of patients included.

We set out to investigate the ocular hemodynamic effects of dorzolamide versus timolol in a larger number of patients with glaucoma or ocular hypertension, based on data previously obtained on the use of these substances.[3–13] In this report the baseline characteristics of the study population are presented. Ocular hemodynamic parameters at baseline were retrospectively compared with those in a group of age-matched healthy control subjects from our database. Special emphasis was placed on the relation between ocular hemodynamic variables and systemic blood pressure in these study groups. The results of the longitudinal study are to be presented in a future report.

## Subjects and Methods

### Patients

After approval by the Ethics Committee of Vienna University School of Medicine of the study protocol, which adhered to the tenets of the Declaration of Helsinki, 140 patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) were included. The baseline characteristics of these patients are shown in Table 1. Inclusion criteria in the present study were the presence of either primary POAG or OHT, with an untreated intraocular pressure (IOP) of 21 mm Hg or more in at least one eye documented on least at three occasions. All patients had to be eligible for antiglaucoma monotherapy. For all patients who had been treated with any topical antiglaucoma drug, a washout period of 2 weeks was set. Any of the following excluded a patient from participation in the trial: exfoliation glaucoma, pigmentary glaucoma, history of acute angle closure, standard deviation (mean deviation [MD]) of more than 10 in visual field testing (Humphrey Field Analyzer, 30-2 program; Carl Zeiss Meditec, Dublin, CA), intraocular surgery or argon laser trabeculoplasty within the past 6 months, ocular inflammation or infection within the past 3 months, bradycardia (heart rate <50 beats/min), second- and third-degree heart block, asthma bronchiale, chronic obstructive pulmonary disease, congestive heart failure, severe renal impairment (creatinine clearance <1.8 L/h), history of hypersensitivity to one of the study drugs or to drugs with similar chemical structure, history of nonresponse of IOP to topical $\beta$-blockers or topical carbonic anhydrase inhibitors, and pregnancy.

The differentiation of POAG and OHT in the patients was based on the criteria of the Ocular Hypertension Treatment Study.[14] An abnormal visual field was accordingly defined as having a glaucoma hemifield test result outside normal limits and/or a corrected pattern standard deviation (CPSD) with $P < 0.05$. In addition, the horizontal and vertical cup/disc (C/D) ratios and the optic disc area were determined (Table 1).

**TABLE 1.** Characteristics of the Study Population

| | POAG | OHT | Healthy Control | *P* |
|---|---|---|---|---|
| Number | 49 | 91 | 102 | |
| Age | 63.0 ± 13.5 | 61.2 ± 13.3 | 63.4 ± 11.1 | 0.39* |
| Male/female | 19/30 | 48/43 | 44/58 | 0.09* |
| IOP | 22.6 ± 2.9 | 23.2 ± 3.8 | 14.5 ± 2.2 | <0.001* |
| SBP (mm Hg) | 141.0 ± 15.8 | 142.8 ± 17.8 | 149.8 ± 13.4 | 0.18* |
| DBP (mm Hg) | 75.7 ± 10.1 | 74.8 ± 11.9 | 76.6 ± 8.3 | 0.36* |
| Ocular perfusion pressure (mm Hg) | 39.0 ± 7.2 | 40.6 ± 9.0 | 51.8 ± 6.3 | <0.001* |
| Pulse rate (min) | 78.1 ± 12.5 | 78.0 ± 11.6 | 77.3 ± 10.3 | 0.52* |
| MD | −1.58 (−11.09 to +2.83) | −0.16 (−5.35 to +4.10) | — | <0.001† |
| Vertical C/D ratio | 0.75 ± 0.11 | 0.59 ± 0.12 | 0.51 ± 0.11 | <0.001* |
| Horizontal C/D ratio | 0.77 ± 0.11 | 0.62 ± 0.11 | 0.52 ± 0.10 | <0.001* |
| Optic disc area ($mm^2$) | 2.58 ± 0.37 | 2.46 ± 0.34 | 2.50 ± 0.32 | 0.12* |

Data are presented as the mean ± SD except for the MD, for which the median (range) is shown.
* Calculated by one-way ANOVA.
† Calculated by Wilcoxon signed rank test.

The baseline characteristics of the patients with glaucoma or ocular hypertension were retrospectively compared with the results in an age-matched control group from our database ($n = 102$). The characteristics of this control group are also presented in Table 1.

## Methods

**Scanning Laser Doppler Flowmetry.** The principles of laser Doppler flowmetry (Heidelberg Retina Flowmeter [HR]; Heidelberg Engineering, Heidelberg, Germany) have been described in detail by Bonner and Nossal.[15] Briefly, vascularized tissue is illuminated by coherent laser light. Scattering by moving red blood cells (RBCs) leads to a frequency shift in the scattered light. In contrast, static scatterers in tissue do not change light frequency, but lead to randomization of light directions impinging on RBCs. This light diffusing in vascularized tissue leads to a broadening of the spectrum of scattered light (Doppler shift power spectrum, DSPS). From this DSPS, the mean RBC velocity, blood volume, and blood flow can be calculated in relative units. These parameters are calculated from the backscattered light for each point during the scanning process. The procedure of data sampling and the confocal optical system are described in detail by Michelson et al.[16] The line sample frequency is 4000 Hz, and frequencies less than 125 Hz are excluded for fast Fourier transform.

From the calculated RBC velocity, the blood volume, and the blood flow, a two-dimensional map of retinal and optic nerve perfusion is created. Hence, these parameters can be quantified in relative units for any image point. In the present study, one 10 × 10-pixel area (100 × 100 $\mu$m) in the cup of the optic disc (CupBF) and one 20 × 20-pixel area (200 × 200 $\mu$m) at the temporal neuroretinal rim (RimBF) were chosen for calculation of hemodynamic parameters. The selection of the measurement areas was based on the method described by Nicolela et al.[17] The neuroretinal rim was measured from images focused on the superficial retina. The cup was measured from images focused on the lamina cribrosa. The measurements were performed in regions without major surface vessels.

Reproducibility is a critical issue with scanning laser Doppler flowmetry.[18,19] Hence, at least two recordings were taken, and the mean of the two values from the best images obtained was calculated. Only flow readings with a coefficient of variation of less than 20% were included in the analysis.

**Laser Interferometric Measurement of Fundus Pulsation.** Pulse synchronous pulsations of the eye fundus were assessed by laser interferometry. The method is described in detail by Schmetterer et al.[20] Briefly, the eye is illuminated by the beam of a single-mode laser diode with a wavelength ($\lambda$) of 783 nm. The light is reflected at both the front surface of the cornea and the fundus. The two reemitted waves produce interference fringes from which the changes in distance between cornea and retina during a cardiac cycle can be calculated. These changes in distance lead to a corresponding variation of the interference order ($\Delta N(t)$) that can be evaluated by counting the fringes moving inward and outward during the cardiac cycle. Changes in optical distance ($\Delta L(t)$), corresponding to the changes in cornea–retina distance, can then be calculated by $\Delta L(t) = \Delta N(t) \cdot \lambda/2$. The maximum distance change is called fundus pulsation amplitude (FPA) and estimates the local pulsatile blood flow.[21,22] Measurements of fundus pulsation amplitude were performed in the fovea to assess pulsatile choroidal blood flow. Again, two measurements were performed at each fundus location, and the mean of the two measurements was calculated. FPAs with a coefficient of variation of more than 20% were not included in the analysis.

**Visual Field Testing.** Visual field testing was performed with the Humphrey Field analyzer (Full Threshold program 30-2; Carl Zeiss Meditec). All patients were experienced in visual field testing, having performed at least three tests in total, one within 3 months of the beginning of the study. All measurements were supervised by an experienced technician. Visual field eligibility criteria were less than 33% false-positive responses, less than 33% false-negative responses, and less than 33% fixation losses.

**Noninvasive Measurement of Systemic Hemodynamics.** Systolic (SBP) and diastolic (DBP) blood pressures were measured on the upper arm by an automated oscillometric device. Mean arterial pressure (MAP) was calculated as ⅓(SBP) + ⅔(DBP). Pulse rate (PR) was automatically recorded from a finger-pulse oximeter (HP-CMS patient monitor; Hewlett Packard, Palo Alto, CA). Ocular perfusion pressure in the sitting position was calculated as ⅔MAP − IOP.

## Data Analyses

Ocular hemodynamic parameters between patients with POAG, patients with OHT, and healthy control subjects were compared by one-way ANOVA. The MD data were tested for normal distribution with the Kolmogorov-Smirnov test. Because data were not normally distributed, the Wilcoxon signed rank test was used for statistical analysis (OHT group versus glaucoma group). Linear regression analysis was performed to determine the correlation between MAP and ocular perfusion pressures and ocular hemodynamic parameters (in arbitrary units [au]) in both study groups. In addition, a multiple regression analysis was performed to characterize determinants of optic nerve head (ONH) blood flow and fundus pulsation amplitude.

**TABLE 2.** Ocular Hemodynamic Parameters in the Disease and Control Groups

| | POAG or OHT | Healthy Control | *P* |
|---|---|---|---|
| RimBF* | 205 ± 92 | 348 ± 104 | <0.001 |
| CupBF* | 315 ± 113 | 533 ± 126 | <0.001 |
| FPA ($\mu$m) | 3.2 ± 0.9 | 3.9 ± 1.1 | <0.001 |

* Data are mean arbitrary units ± SD.

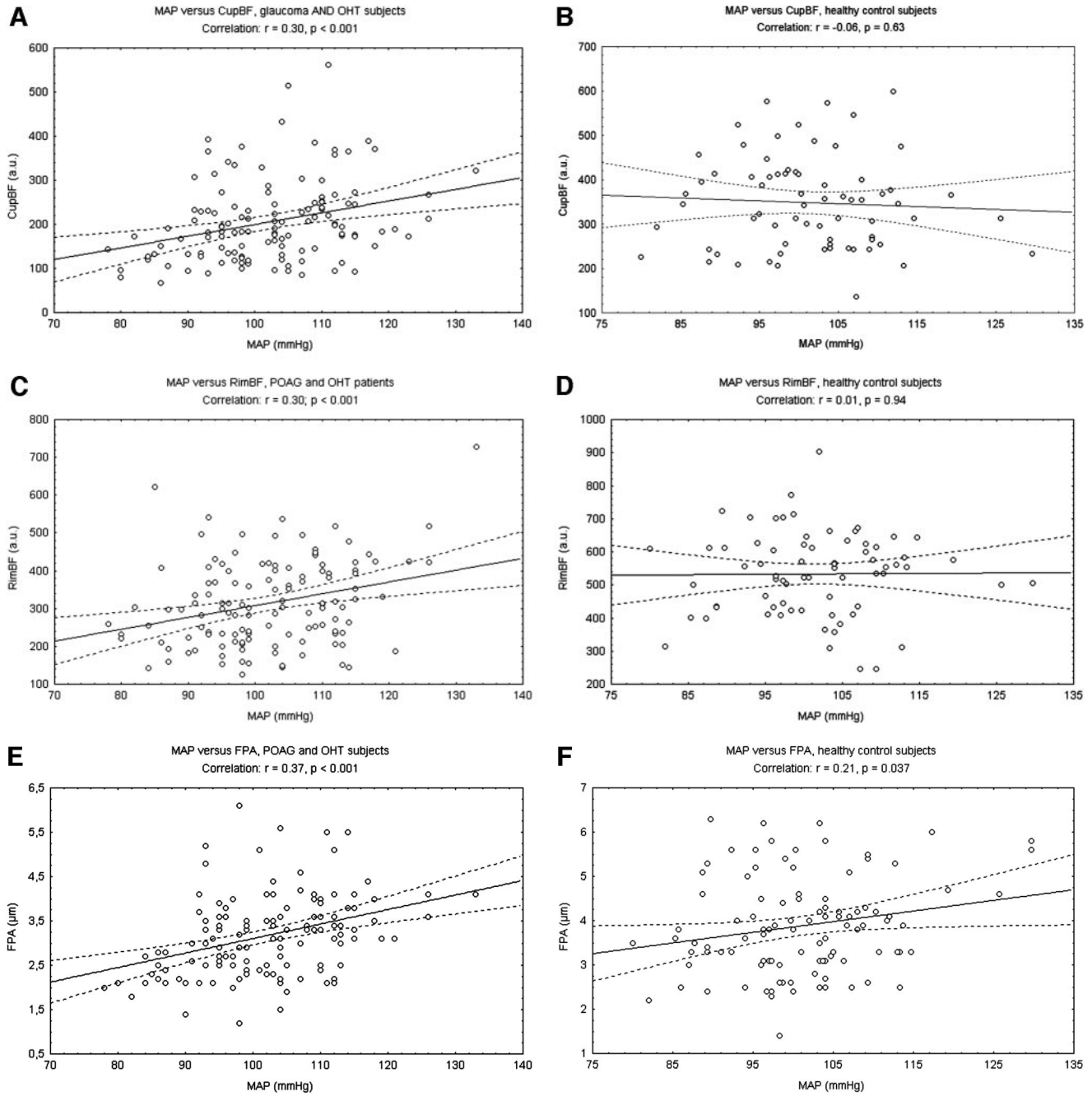


**FIGURE 1.** Linear correlation (*solid lines*) of (**A**, **B**) CupBF, (**C**, **D**) RimBF, and (**E**, **F**) FPA with mean arterial pressure (MAP). Data are shown separately for (**A**, **C**, **E**) patients with POAG or OHT ($n = 140$) and (**B**, **D**, **F**) healthy control subjects ($n = 102$). *Dashed lines*: 95% confidence intervals.

Data are presented as the mean ± SD. The level of significance was set at $P = 0.05$.

## RESULTS

There were no significant differences in age, gender, or systemic hemodynamics between the study groups (Table 1). IOP was higher in patients with POAG or OHT than in healthy control subjects. Accordingly, the POAG and OHT groups had lower mean ocular perfusion pressure than did the healthy control group.

Using scanning laser Doppler flowmetry in patients with POAG or OHT, 125 (89%) and 127 (91%) blood flow readings, with a coefficient of variation of less than 20% were obtained at the neuroretinal rim and the cup, respectively. In healthy control subjects, 71 (69%) measurements fulfilled this criterion at both locations under study. The coefficient of variation of FPA measurements was less than 20% in 134 (96%) of the patients with POAG or OHT and in all the control subjects.

Results from measurements with the laser Doppler flowmeter and the laser interferometer are presented in Table 2 for both study groups. All ocular hemodynamic parameters were significantly lower in the patient groups than in the healthy control group.

A significant association was observed between ocular hemodynamic parameters and MAP in the groups of patients (Fig. 1). The correlation coefficient was highest for FPA and MAP and lowest for RimBF and MAP. A 10-mm Hg increase in MAP

**TABLE 3.** Ocular Hemodynamic Parameters in Patients with POAG or OHT

| | POAG | OHT | *P* |
|---|---|---|---|
| RimBF* | 192 ± 71 | 212 ± 101 | 0.25 |
| CupBF* | 287 ± 51 | 333 ± 111 | 0.07 |
| FPA ($\mu$m) | 3.0 ± 0.8 | 3.3 ± 0.9 | 0.15 |

* Data are mean arbitrary units ± SD.

was associated with a 26-au increase in CupBF, a 29-au increase in RimBF and a 0.3-$\mu$m increase in FPA. By contrast, no significant association was observed between MAP and either CupBF or RimBF in healthy control subjects. The correlation between MAP and FPA was significant in healthy subjects, but the correlation coefficient was smaller than in the POAG or OHT groups. A 10-mm Hg increase in MAP was associated with a 0.2-$\mu$m increase in FPA. The difference in the correlation coefficients between MAP and FPA in the two study populations, however, was not significant ($P = 0.19$). The differences in the correlation coefficients between CupBF and MAP ($P = 0.015$) and RimBF and MAP ($P = 0.047$) was statistically significant between the POAG/OHT groups and the healthy control group. When correlation analysis between ocular hemodynamic parameters and MAP were performed separately for the POAG and OHT groups, correlation coefficients were generally higher in the former group. This effect tended to be significant for the correlation between RimBF and MAP (POAG: $r = 0.45$; $P = 0.002$; OHT: $r = 0.16$; $P = 0.149$; $P = 0.07$ between groups). The correlations between CupBF and MAP (POAG: $r = 0.36$; $P = 0.016$; OHT: $r = 0.23$; $P = 0.042$; $P = 0.43$ between groups) and FPA and MAP (POAG: $r = 0.39$; $P = 0.007$; OHT: $r = 0.35$; $P = 0.001$; $P = 0.80$ between groups) was comparable between the two patient groups.

BP, PR, and IOP were comparable between the POAG and OHT groups (data not shown). CupBF, RimBF, and FPA tended to be higher in patients with POAG than in those with OHT, but none of these effects reached the level of significance (Table 3).

The results of multiple regression analyses are shown in Table 4. CupBF and FPA showed a significant correlation with MAP and ocular perfusion pressure in the POAG and OHT groups. RimBF was correlated with MAP and ocular perfusion pressure only in the POAG group. By contrast, only FPA was dependent on MAP in the group of healthy control subjects. All ocular hemodynamic parameters were independent of the other variables in the three groups.

## DISCUSSION

In the present report, the baseline characteristics of a study population participating in a clinical trial on the ocular hemodynamic effects of dorzolamide and timolol are presented. Compared with a group of age-matched healthy control subjects, these patients with POAG or OHT had lower blood flow in the ONH cup and at the neurovascular rim, as assessed with scanning laser Doppler flowmetry. In addition, these patients had lower FPA, indicating reduced pulsatile choroidal blood flow in POAG and OHT. Reduced blood flow to the posterior pole of the eye has been reported in many studies in which a variety of different techniques were used for the assessment of ocular blood flow.[17,23–29]

The present study, however, shows that these reduced ocular blood flow parameters were also observed in patients after a 2-week washout period of topical antiglaucoma drugs, indicating that this observation is not related to drug-induced vasoconstrictor effects. Only a few studies have shown that lower ocular blood flow parameters are observed in patients with untreated glaucoma compared with healthy control subjects.[23,27]

In the present study, it is noteworthy that there was no significant difference in ocular blood flow parameters between patients with POAG and those with OHT. This finding is in line with the results of other studies indicating that vascular abnormalities are an early event in the process of glaucoma. Laser Doppler flowmetry showed no significant differences in blood flow parameters in the ONH and the choroid between patients with POAG and those with suspected glaucoma.[30] In the same study, blood flow in the superotemporal rim, the inferotemporal rim, and the cup was significantly lower in those with suspected glaucoma than in healthy control subjects. Abnormalities in ONH perfusion in patients with untreated OHT have also been proposed based on measurements of Doppler broadening, using laser Doppler technology.[31] Kerr et al.[27] reported that patients with untreated POAG have a reduction in lamina cribrosa and temporal neuroretinal RimBF compared with patients with OHT; however, a healthy control group was not included in this study. In our group of patients with OHT, an increased vertical and horizontal C/D ratio was found, compared with the healthy control group, which is related to the fact that care was taken to include as many patients with suspected glaucoma in the OHT group as possible. Our results may therefore indicate that reduced ONH blood flow is an early event in glaucoma, as has been speculated.[30] To answer this question definitely, a longitudinal study in patients with OHT is needed.

An important result of the present study is that MAP was a determinant of RimBF and CupBF in patients with POAG or OHT but not in healthy control subjects. Likewise, the association between FPA and MAP was higher in the POAG and OHT groups than in the control group. Correlation coefficients were generally small in the present study, however, which may be related to the variability in the HRF data but also to local variations in ONH blood flow. An abnormal association between ONH blood flow, as assessed with laser Doppler flowmetry and systemic blood pressure, was reported by Grunwald et al.[32] Compared with that study the correlation lines in the present study are less steep. Whether this is related to the different systems used for assessment of ONH perfusion is unclear. It should be mentioned, however, that the present

**TABLE 4.** Multiple Regression Analyses Showing Comparison of Ocular Hemodynamic Parameters with Patients' Characteristics and Ocular Measurements

| | RimBF | CupBF | FPA |
|---|---|---|---|
| POAG | | | |
| Age | 0.230 | 0.170 | 0.400 |
| Mean BP | 0.003 | 0.022 | 0.009 |
| Ocular perfusion pressure | 0.002 | 0.025 | 0.011 |
| PR | 0.770 | 0.450 | 0.920 |
| IOP | 0.880 | 0.370 | 0.950 |
| MD | 0.160 | 0.090 | 0.070 |
| OHT | | | |
| Age | 0.130 | 0.110 | 0.450 |
| Mean BP | 0.150 | 0.040 | 0.003 |
| Ocular perfusion pressure | 0.092 | 0.035 | 0.006 |
| PR | 0.750 | 0.450 | 0.910 |
| IOP | 0.910 | 0.400 | 0.970 |
| MD | 0.580 | 0.600 | 0.110 |
| Healthy control | | | |
| Age | 0.120 | 0.240 | 0.280 |
| Mean BP | 0.870 | 0.750 | 0.047 |
| Ocular perfusion pressure | 0.730 | 0.660 | 0.033 |
| PR | 0.670 | 0.720 | 0.610 |
| IOP | 0.130 | 0.210 | 0.150 |

Data are probabilities.

paper reports on a much larger study cohort without current topical antiglaucoma treatment. In another study, an association between end diastolic blood velocity in the ophthalmic artery and the central retinal artery and ocular perfusion pressure was observed in patients with progressive glaucoma, but not in patients with nonprogressive glaucoma or healthy control subjects.[33]

This abnormal association between ocular blood flow parameters and MAP is compatible with previous studies indicating abnormal blood flow autoregulation in patients with POAG or OHT, based on experiments examining short-term changes in ocular perfusion pressure. During changes in posture, patients with glaucoma exhibit an abnormal response in blood velocities in the central retinal artery.[34] A study using the blue-field entoptic technique suggested abnormal retinal blood flow regulation during an artificial change in IOP.[35] Abnormalities in choroidal blood flow autoregulation were suggested based on experiments using visual evoked potentials,[36] pneumotonometry,[37] and combined videoangiography with oculo-oscillo-dynamography.[38]

The association between FPA and MAP in both the patient groups and the age-matched control group is in keeping with the results reported previously in healthy young subjects.[39] However, the regression line appears to be steeper than in the cohort of younger subjects. Recent studies in animals[40] and humans indicate[41–43] that choroidal blood flow is maintained over a wide range of ocular perfusion pressures. Whether our results can be interpreted as a partial loss of choroidal blood flow regulation with age remains to be established.

There has been a long-standing discussion of whether vascular events are a cause of axon and retinal ganglion cell loss or a consequence of reduced nutritional requirements caused by axonal and retinal ganglion cell injury. Obviously, a cross-sectional study is not capable of finally answering this important question. However, the abnormal association between ocular blood flow parameters and systemic blood pressure, as observed in the present study, is difficult to explain based on the hypothesis that reduced blood flow is a sole consequence of ONH damage.

In a previous study we observed that, in patients with POAG, CupBF, and RimBF declined with increasing visual field defect.[29] This relationship of MD to blood flow was not confirmed in the present study, perhaps because patients with glaucoma at more advanced stages were included in our previous study.

An important limitation of the present study is that we did not measure central corneal thickness in our study population. Accordingly, we are not able to distinguish between patients with OHT and pseudo-OHT. Based on pooled data of corneal thickness in patients with OHT[44] and normal subjects, we calculated that less than 10% of our patients with OHT were likely to have pseudo-OHT. Hence, this limitation of the present study does not appear to be severe with regard to the main conclusions drawn.

In conclusion, the present study confirmed that ocular hemodynamic parameters are reduced in patients with POAG and OHT compared with healthy age-matched control subjects. The main result of the present trial is the abnormal association between ONH BF and BP. It is important to mention again that these results were observed after a 2-week washout of the topical antiglaucoma medication, showing that vascular abnormalities observed in patients with POAG or OHT were not a consequence of pharmacologic intervention.

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