Choroidal Blood Flow Response to Isometric Exercise in Glaucoma Patients and Patients with Ocular Hypertension

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PURPOSE. To analyze submacular choroidal blood flow (ChBF) response to isometric exercise in untreated patients with glaucoma and ocular hypertension.

METHODS. ChBF was examined by means of confocal laser Doppler flowmetry during 5 minutes of baseline, during 90 seconds of isometric exercise with a Martin’s vigiometer and during 15 minutes of recovery. Values from one randomly chosen eye of 45 healthy subjects, the eye with more advanced damage in 45 primary open-angle glaucoma (POAG) patients, and the eye with higher native intraocular pressure in 45 patients with ocular hypertension (OHT) were acquired, and parameters of ChBF as well as blood pressure response were analyzed.

RESULTS. Healthy eyes demonstrated higher ChBF at baseline than did the eyes in the other group (51.26 ± 1487, 4186 ± 1011, and 4437 ± 1372 arbitrary units, ANOVA P = 0.003). Both mean and diastolic arterial blood pressures at baseline were lower in POAG patients than in those with OHT and healthy controls (P < 0.03); however, the response of mean blood pressure to isometric exercise was comparable across groups (P = 0.79). The ChBF response to exercise was stronger in the POAG group (ANOVA P = 0.02), it was twice as high as in the controls (+8.1% ± 8.0% vs. +3.7% ± 6.7%; P = 0.007) and borderline higher than in the OHT patients (+5.0% ± 8.0%; P = 0.051).

CONCLUSIONS. Baseline ChBF was lower in both the POAG and the OHT patients, compared with that in the controls. The stronger increase in ChBF in POAG patients in the face of an exercise-induced blood pressure increase indicates less active regulatory capacity in glaucoma patients (ClinicalTrials.gov number, NCT00430209). (Invest Ophthalmol Vis Sci. 2011;52: 7068–7073) DOI:10.1167/iovs.11-7758

Ocular blood flow fluctuations have been, apart from intraocular pressure (IOP), implicated as the major risk factor for glaucoma.2,3 Perfusion pressure and local resistance are major determinants of blood flow through an organ, ensuring an adequate supply of oxygen and nutrients to the tissue. Autoregulation represents an ability of the vascular bed to maintain constant blood flow, despite changes in perfusion pressure, through fine tuning of the local resistance. Choroidal circulation in healthy humans is able to keep the perfusion relatively constant in the face of changing intraocular and/or blood pressure.3–6 Various methods have been applied to test an influence of exercise on choroidal circulation, most commonly squatting,1,7–15 cycling,16–19 or similar methods.20 An isometric hand-grip test is a specific, sensitive, reproducible, simple, and noninvasive test of sympathetic function with relatively well-studied reflex pathways21 and has been repeatedly used in studies of the ocular circulation.22–24 Despite the large number of studies dealing with the response of choroidal circulation to exercise, only one study addressed this question directly in glaucoma patients,25 but merely as a substudy and with no direct comparison of this response to the control group. Knowing that blood pressure variability represents an independent risk factor for glaucoma,25–29 we were interesting in investigating the behavior of choroidal circulation of patients with primary open-angle glaucoma (POAG) in the face of changing blood pressure and to compare it directly to that of healthy controls and to that of OHT patients, who, despite an increased IOP, did not develop glaucomatous damage.

METHODS

Subjects

Consecutive POAG patients and OHT patients were recruited for the study from glaucoma consultations at the University Eye Clinic Basel. After approval by the ethics committee, we obtained informed consent from our subjects. The study complied with the Declaration of Helsinki. Healthy controls were recruited through ads in local newspapers. Subjects were screened for ocular and systemic diseases. Newly diagnosed and therapy-naive POAG and OHT patients meeting study criteria underwent study examinations, patients on IOP-lowering therapy were first subjected to a 4-week washout phase. A detailed medical and ophthalmic history was recorded, and all subjects completed an ophthalmic examination. POAG was diagnosed based on glaucomatous optic disc cupping (in particular, thinning of the inferior and/or superior rim, remodeling of lamina cribrosa, and, in some cases, cup-to-disc ratio asymmetry) and on matching visual field defects (three adjacent point defects of >5 dB, one of them >10 dB, on one side of the horizontal meridian, or two adjacent point defects >10 dB). Naïve IOP was neither an exclusion nor and inclusion criterion for POAG diagnosis. In contrast, at least two daily readings of naïve IOP of equal or above 21 mm Hg, in absence of disc or visual field damage, were required for the diagnosis of OHT. All participants with diabetes mellitus; unstable arterial hypertension; unstable dyslipidemia; drug or alcohol abuse or a smoking habit; a history of eye surgery except...
pseudophakia, high ametropia (spherical equivalent, $<-5$ or $>+3$ D); astigmatism above 2 D; significant cataract, pigment, or pseudoxefoliation (PEX) dispersion syndrome; a history of an acute glaucoma episode; and any form of secondary glaucoma were excluded from the study. In the POAG group, the eye in each subject with the most advanced damage (higher mean visual field [VF] defect and thinner peripapillary retinal nerve fiber layer [RNFL]); in the OHT group, the eye with the highest average IOP; and, in healthy controls, one randomly selected eye per subject was entered into the analysis. If the fixation with the selected eye was poor, the other eye was tested, provided that the inclusion criteria were met.

**Submacular Choroidal Blood Flow**
Submacular choroidal blood flow (ChBF) was determined by using a method based on the laser Doppler flowmetry (LDF) technique. The optical system is based on a confocal arrangement. A polarized laser source ($\lambda = 785$ nm, $100$ mW) is relayed with a 1:1 optical system (laser beam at the cornea: width $=1.3$ mm, power $=90$ $\mu W$) and focused on the subject's retina (spot in the retinal image plane, $10-20$ $\mu m$ in diameter; optical thickness of the confocal layer, $300$ $\mu m$). The point laser source, the point of illumination of the fovea, and the detecting optical fiber are located in conjugated planes. The scattered light is collected by an optical system organized with six fibers arranged circularly around the central fixation point along a circle of diameter of $180$ $\mu m$ (within the avascular zone of the fovea). The photocurrent from the photodetector is Fourier transformed and the hemodynamic parameters, flow, volume, and velocity are processed as outlined above. Each parameter varies linearly with respect to changes in blood flow. Subjects fixated the red light spot within the ocular and adjusted the focus by turning the ocular. The ocular-to-cornea distance was set between 1.5 and 2 cm. Constant, very low, artificial room illumination was used throughout all the experiments. Stable DC (direct current) during recording was used as a criterion of proper fixation.

**Systemic Blood Pressure**
Blood pressure was measured with a finger device (Finometer, ver. 1.21; Finapres Medical Systems BV, Arnhem, The Netherlands). This device measures the blood pressure in the finger noninvasively and continuously. As the finger arterial pressure may differ from intra-brachial pressure, the device uses an additional return-to-flow systolic pressure measurement on the ipsilateral upper arm for an individual calibration of the reconstructed brachial pressure. It measures the brachial pressure in a traditional way and corrects the finger pressure accordingly. According to Guelen et al. the calculated estimations deviate from the intra-arterially measured intrabrachial pressures by $-1.1 \pm 10.7$. $-0.2 \pm 6.8$, and $-1.5 \pm 6.6$ Hg for the systolic, diastolic, and mean blood pressures, respectively. Mean blood pressure was calculated as diastolic BP plus one third of the systolic minus diastolic BP.

**IOP, Visual Field, and Retinal Nerve Fiber Layer Thickness**
IOP was measured by Goldmann applanation tonometry, VFs by automated perimetry (Octopus 101; Haag Streit International, Köniz, Switzerland), and RNFL thickness by optical coherence tomography (OCT RNFL, Stratus OCT; Carl Zeiss Meditec, Oberkochen, Germany).

**Isometric Hand-Grip Test**
An isometric handgrip test was performed in all subjects. A bulb dynamometer (Martin Vigorimeter; BCB Ltd., Cardiff, Wales, UK) was used in the present study, as detailed elsewhere. Candidates were instructed to briefly exert maximum compressive force with the dominant hand, evaluating the maximum voluntary contraction. After 20 minutes of recovery, the patients were asked to maintain hand-grip contraction at 50% of the predetermined maximum voluntary contrac-

**Experimental Procedures**
Participants were instructed to abstain from a large meal, alcohol consumption (including alcohol-containing products and drugs), and physical exercise for 24 hours before the measurements. One eye per subject was examined. On the day of the experiments, eyes had been free of any ocular therapy for at least 4 weeks. IOP was measured first. Afterward, measurements of LDF and BP were performed simultaneously. First, a 5-minute recording of baseline arterial blood pressure and submacular ChBF was taken. Then, without changing position, subjects were asked to perform a handgrip test for 90 seconds, while continuously measuring LDF and BP. Measurements of LDF and BP also continued during 15 minutes of recovery. LDF and BP data were collapsed to produce one value for the 5-minute baseline period, one for the 90-second exercise phase, and three (one every 5 minutes, arbitrarily chosen) for the 15-minute recovery phase. At the end of this time, an IOP reading was taken again.

**Data Analysis**
Difference of baseline parameters across groups was evaluated by one-way analysis of variance (ANOVA). Change in relation to baseline during the exercise phase was analyzed for the LDF flow and mean BP, also with one-way ANOVA. Correlations were tested during the exercise phase as well as during the recovery phase by linear regression analysis. An association of the LDF flow (its baseline value and change during exercise) with measures of glaucomatous damage (OCT RNFL thickness and visual field mean defect [MD]) was performed by means of linear and multiple regression analyses. The behavior of LDF velocity and volume during the experimental phases is presented graphically in the figures. Ocular perfusion pressure (OPP) at baseline was calculated according to the formula OPP $= [2/3] \times$ MAP (mean arterial pressure) $-\text{IOP}$.

**RESULTS**
Patients with POAG or OHT were consecutively recruited from the outpatient and/or inpatient glaucoma consultations at the University Hospital Basel. Recruitment continued until 45 subjects were entered in each group. The primary recruitment goal per protocol was set at 50 subjects per group. Subjects and patients whose fixation during the LDF examination was unstable and inadequate were excluded from further analysis.

Demographic data of study subjects and baseline parameter values are presented in Table 1. At baseline, POAG patients and OHT patients had lower choroidal LDF flow than did the healthy controls, and POAG patients had lower choroidal LDF volume than that of the healthy controls. Average DC value, as an expression of optical scattering properties of the tissue that can systematically influence the LDF parameters flow and volume, was significantly different across the three groups (lowest in the healthy controls; ANOVA $P = 0.03$). Unfortunately, there is no known technical solution to this problem, and it can be alleviated merely by calculating the fit between the DC and the respective LDF parameter and partializing the influence of the DC level. This procedure is statistical in nature and should be performed for each given set of subjects who are recorded under similar conditions. In essence, using DC as a covariate achieves exactly this goal; it corrects statistically for the influence of the DC level. For this reason, analysis of these parameters was performed again, with baseline DC values as a covariate, thus correcting for its influence. The results confirmed the original findings (for LDF flow, ANCOVA $P = 0.02$; for LDF volume, ANCOVA $P = 0.02$).

Systemic antihypertensive therapy was well balanced and comparable across groups (data not shown). Diastolic and
mean arterial blood pressures were significantly lower at baseline in POAG patients than in both other groups, OPP was higher in the control group than in the other two groups (Table 1). The ANCOVA described in the previous paragraph was also performed with baseline OPP as the second covariate, and the results confirmed the previous findings (for LDF flow, ANCOVA $P = 0.02$; for LDF volume, ANCOVA $P = 0.01$), indicating that baseline blood flow differences were based neither on different optical scattering properties nor on differences in OPP.

The percentage change from baseline in choroidal LDF flow during exercise was $+3.7\% \pm 6.7\%$, $+8.1\% \pm 8.0\%$, and $+5.0\% \pm 8.0\%$, in controls and POAG and OHT patients, respectively (ANCOVA $P = 0.02$; post hoc least significant difference [LSD] test: controls versus POAG, $P = 0.007$; OHT versus POAG, $P = 0.051$), with DC value changes comparable across groups. The percentage change from baseline in mean blood pressure during exercise was similar in the three groups: $+9.1\% \pm 5.3\%$, $+9.8\% \pm 5.0\%$, and $+9.6\% \pm 5.6\%$, respectively (ANCOVA $P = 0.79$). Also, the percentage change in OPP from baseline was comparable across groups (for reasons detailed in the Discussion section, IOP was not measured during the exercise phase; baseline IOP was used for this calculation): $+11.7\% \pm 6.9\%$, $+14.0\% \pm 7.6\%$, and $+14.2\% \pm 8.2\%$, respectively (ANCOVA $P = 0.22$). With OPP change used as the covariate, change in choroidal LDF flow remained significantly different across groups (ANCOVA $P = 0.026$; post hoc LSD test controls versus POAG $P = 0.005$, OHT versus POAG $P = 0.026$).

Figure 1 presents OPP and LDF flow values during the experimental phases. Linear regression analysis was performed between the change in LDF flow and the change in OPP during the exercise phase (all eyes taken together: $r = 0.28$, $P < 0.01$; individual groups: controls, $r = 0.27$, $P = 0.07$; POAG patients, $r = 0.28$, $P = 0.07$; and OHT patients, $r = 0.28$, $P = 0.07$). Linear regression analysis was also performed in all study subjects together, between the percentage change in LDF flow and the change in mean blood pressure during the exercise ($r = 0.25$, $P < 0.01$). The relative change in percentage of baseline of LDF flow was calculated also for the three recovery 5-minute periods, and the regression analysis, with the mean blood pressure percentage change versus baseline during recovery showing a weak positive correlation ($r = 0.16$, $P < 0.01$). Correlation analysis across groups (controls/POAG/OHT) revealed no differences in group behavior in this regard, either during exercise or during the recovery period (data not shown).

Furthermore, we analyzed an association between the LDF flow and the measures of glaucomatous damage within the POAG group only. Baseline LDF flow correlated significantly with an average OCT RNFL thickness ($r = 0.41$, $P < 0.01$), but not with visual field MD ($r = -0.26$, $P = 0.09$). The change in LDF flow during exercise correlated neither with RNFL thickness nor with MD. Interestingly, to correct for the DC influence on baseline LDF flow, a multiple regression analysis was performed with OCT RNFL thickness as a dependent and LDF flow and DC as two independent variables. The results in the whole model were significant ($P < 0.01$; $R = 0.51$). Both

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (1)</th>
<th>POAG (2)</th>
<th>OHT (3)</th>
<th>Statistics (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58 ± 8</td>
<td>61 ± 10</td>
<td>62 ± 9</td>
<td>$P = 0.07$</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/21</td>
<td>19/26</td>
<td>25/20</td>
<td></td>
</tr>
<tr>
<td>Average peripapillary RNFL:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCT, µm</td>
<td>99 ± 12</td>
<td>79 ± 16</td>
<td>95 ± 11</td>
<td>$P &lt; 0.001$ (post hoc LSD test: 1 vs. 2 and 2 vs. 3 significant)</td>
</tr>
<tr>
<td>Visual field MD, dB</td>
<td>0.8 ± 1.6</td>
<td>2.2 ± 2.3</td>
<td>0.3 ± 1.6</td>
<td>$P &lt; 0.001$ (post hoc LSD test: 1 vs. 2 and 2 vs. 3 significant)</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>15 ± 2</td>
<td>17 ± 5</td>
<td>22 ± 4</td>
<td>$P &lt; 0.001$ (all post hoc LSD test pairs significant)</td>
</tr>
<tr>
<td>Choroidal LDF velocity, Hz</td>
<td>3998 ± 1362</td>
<td>5696 ± 1095</td>
<td>3682 ± 1191</td>
<td>$P = 0.38$</td>
</tr>
<tr>
<td>Choroidal LDF volume, AU</td>
<td>1547 ± 240</td>
<td>1208 ± 283</td>
<td>1264 ± 248</td>
<td>$P = 0.04$ (post hoc LSD test: 1 vs. 2 significant)</td>
</tr>
<tr>
<td>Choroidal LDF flow, AU</td>
<td>5126 ± 1487</td>
<td>4186 ± 1011</td>
<td>4437 ± 1372</td>
<td>$P = 0.003$ (post hoc LSD test: 1 vs. 2 and 1 vs. 3 significant)</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>143 ± 20</td>
<td>137 ± 22</td>
<td>148 ± 22</td>
<td>$P = 0.04$ (post hoc LSD test: 2 vs. 3 significant)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83 ± 11</td>
<td>77 ± 15</td>
<td>85 ± 14</td>
<td>$P = 0.03$ (post hoc LSD test: 1 vs. 2 and 2 vs. 3 significant)</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>103 ± 13</td>
<td>97 ± 15</td>
<td>105 ± 16</td>
<td>$P = 0.03$ (post hoc LSD test: 1 vs. 2 and 2 vs. 3 significant)</td>
</tr>
<tr>
<td>Ocular perfusion pressure, mm Hg</td>
<td>54 ± 9</td>
<td>48 ± 11</td>
<td>49 ± 10</td>
<td>$P = 0.007$ (post hoc LSD test: 1 vs. 2 and 1 vs. 3 significant)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD, with results of the one-way ANOVA between groups.
DISCUSSION

In the present study, we analyzed the response of choroidal circulation during a hand-grip test in untreated POAG patients and compared it to the response in healthy controls and untreated OHT patients.

At baseline, ChBF expressed as the LDF flow parameter was decreased both in POAG and OHT patients, compared with healthy controls, an effect independent of optical tissue-scattering properties. It has been shown by various methods that glaucoma patients demonstrate decreased and unstable choroidal perfusion, even in the absence of provocation tests. Our finding seems to be in line with previous results. This altered perfusion may be in part a consequence of the lower blood pressure, in that diastolic and mean blood pressure at baseline were indeed lower than in healthy controls.

At the end of the recovery period, in comparison to baseline, IOP decreased −1.4 ± 2.0 mm Hg in controls and −1.2 ± 4.8 mm Hg in OHT patients and increased +0.2 ± 3.6 mm Hg in the POAG group (ANOVA \( P = 0.08 \)).

OHT patients also demonstrated 14% lower perfusion on average than healthy controls, despite comparable blood pressure levels. It is likely that an increased IOP in the OHT group can be held responsible for this finding. According to Polska et al., acute IOP changes outweigh blood pressure changes in their effect on blood flow regulation. This, however, is not necessarily true of basal blood flow. On the other hand, it is plausible that an increased blood pressure, compared with POAG patients, in fact acts protectively and prevents glaucomatous damage. However, it should be stressed that the present study was not specifically designed to analyze differences in blood pressure levels between the groups. Although antihypertensive medications were used in less than one third of patients in each group and were well balanced across groups, an ideal design for this purpose would have been to include only completely therapy-free patients, similar to what was achieved with the ocular medications. One should also keep in mind that despite the fact that the ANCOVA model for LDF flow at baseline and with baseline OPP, as a covariate did demonstrate significant differences across groups, at baseline, LDF flow was indeed 14% lower in the OHT group than in controls, but the OPP was 9% lower in the OHT group than in the controls. Similarly, LDF flow was 18% lower in the POAG group than in the controls, but the OPP was 11% lower in the POAG group than in the controls.

Despite an almost identical increase of 9% to 10% in mean blood pressure during the exercise phase in all three groups, POAG patients demonstrated more than double the increase in ChBF compared with the healthy controls (8.1% vs. 3.7%). It is rather unlikely that this result is attributable only to a lower baseline. OHT patients had a comparably low baseline as well and still increased merely 5% on average, a borderline difference from the POAG patients (and significantly different if OPP change from baseline was included in the model as a covariate). In the OHT group, although an increased IOP may influence choroidal perfusion at baseline, the underlying vascular regulatory mechanisms seemed to be comparable to those of the healthy controls. In all studies comparing a healthy choroidal response to exercise to a pathologic one, it was the pathologic one that was higher, despite the comparable changes in blood pressure: This was the case in pseudophakic eyes undergoing cataract surgery, in patients with inactive central serous chorioretinopathy, in patients with neovascular age-related macular degeneration (AMD), in patients with diabetic retinopathy, and even in smokers. All these studies used squatting as an exercise, and squatting produces a much higher increase in blood pressure on average than does the hand-grip test. This, and the dry rather than neovascular AMD, could explain why Metelitsina et al. did not find any differences in their study. We also used a hand-grip test for several reasons: In an elderly glaucoma population, squatting can be a challenge, and a hand-grip test has a less detrimental effect on the ability to fixate on a laser target than squatting. Good fixation is a prerequisite for appropriate LDF measurements. For similar reasons, we did not interrupt the LDF measurements at the peak of the exercise to measure IOP. Refixation after the IOP reading for the continuation of LDF measurements and indeed the very maintaining of an adequate hand grip for a prolonged period to measure IOP would have been likely to result in relevant loss of data quality. The consequence was that OPP could not be calculated during the exercise. In the study by Polska et al., the IOP increase was around 3 mm Hg in healthy young subjects during the first minute of squatting, which is an intense exercise and thus is more likely than the hand-grip exercise, associated with the short-term Valsalva phenomenon, to lead to an IOP increase. On the other hand, a decrease in IOP with exercise has been demonstrated in glaucoma patients. It remains an open question whether IOP changes during the exercise contributed to observed LDF flow differences between groups. However, based on the ANCOVA
results, baseline flow differences were statistically independent of OPP differences between groups.

Squatting for 6 minutes typically induces a 12% to 16% increase in subfoveal ChBF in healthy subjects, with an increase in OPP of approximately 60%.1,2 With the hand grip exercise in our cohort the increase in mean blood pressure was much more modest, approximately 9%. The strongest increase in blood pressure took place in the first 45 to 60 seconds, and after that time, blood pressure tended to remain constant and stable. It should be emphasized, however, that the exercise was performed in fixed time limits and was not driven by reaching the blood pressure plateau. Despite this modest increase, we could detect the difference in the response of the POAG group. It is plausible that revealed differences would have been larger in the face of a larger blood pressure increase. Moreover, when individual LDF flow change in relation to baseline both in the exercise and in the recovery phase, there were no relevant correlation differences between the groups.

Nevertheless, as a group, POAG patients did demonstrate a significantly higher LDF flow increase in the face of the comparable OPP change, and this difference remained clearly significant also when the OPP change was included in the ANCOVA model as a covariate. It seems, in reference and in analogy to the previously mentioned studies, that a pattern emerges. In various pathologic conditions, vessels of submacular choriocapillaris, faced with an increased perfusion pressure, react less actively and simply conduct an increased amount of blood. It is at present unclear what the underlying cause of this disorder might be. A possible explanation is a disturbance of the nitric oxide and/or endothelin-1 regulation, as both substances are involved in the choroidal response to exercise.12,13

Figure 2 demonstrates a relative contribution of the velocity and volume to the overall blood flow change in the choroid during the exercise and the recovery phase. Although no differences between the groups was detected, it is interesting to observe how during the exercise phase it is the velocity increase that explains most of the flow increase, whereas volume contributes very modestly at best. In contrast, in the recovery phase, it seems that new vessels are being recruited and opened for flow in the choriocapillaris, which decreases the blood velocity while increasing the blood volume and keeping the overall flow slightly above the baseline even 15 minutes after cessation of the exercise. Similar behavior with shorter recovery measurements can indeed be found in the literature of other groups,4 but also in our group.23 It is at present unclear whether this observation could help us better understand the underlying vascular physiology of the choroid.

Correlation between the change from baseline of LDF flow and of mean BP during the exercise phase and especially during the recovery phase was modest at best. Weak correlation indicates a certain autoregulatory capacity of the choroid, which is in keeping with the previous studies.5–8 Also, here no differences between the groups were detected.

Baseline LDF flow correlated significantly with an average OCT RNFL thickness. Although these two entities are not necessarily directly related, submacular ChBF and its alterations could be viewed as an indicator of disturbed perfusion in the given eye, which in turn might have lead to glaucomatous damage and thinning of the RNFL. On the other hand, RNFL thinning in glaucoma is associated with macular thinning,41 which in turn could influence optical scattering properties and DC levels. Interestingly, in a multiple regression model, when LDF flow was corrected for DC as a measure of tissue optical scattering properties, both parameters correlated significantly with OCT RNFL thickness. The thicker the RNFL, the less light, on average, reached the photodetector, which seems plausible; moreover, the thinner the RNFL, the lower the LDF flow. Such alteration can either be primary, and perhaps contribute to the glaucomatous damage, or it can be secondary to less tissue demand. In view of the missing correlation of the change-from-baseline LDF flow during exercise and the OCT RNFL thickness, the latter explanation seems more plausible. Neither the baseline LDF flow nor its change from baseline correlated with visual field MD, perhaps due to the discrepancy between the linear nature of the LDF flow parameter and the logarithmic nature of the visual field mean defect, expressed in decibels.

In that ours is a tertiary referral center specializing in ocular vascular disorders, it is likely that in our cohort of POAG patients there was a bias toward non-IOP-related mechanisms of glaucomatous damage. Indeed, relatively low mean naive IOP in our POAG patients indicates a certain shift toward “normal” tension glaucoma. Thus, the results of the present study may be limited to POAG patients with moderate IOP levels.

It is unlikely that the increased variability in ChBF was caused by unstable fixation in the POAG patients. In none of the patients was the central fixation jeopardized by glaucomatous damage. No fixation deficit was observed in any of the examined subjects, since poor fixators were excluded.

The present study was cross-sectional. Further longitudinal studies are needed, to elucidate possible causal relationships between the analyzed parameters.

At baseline condition, the three groups were significantly different from each other in respect to their IOP, LDF flow, blood pressure, and ocular perfusion pressure, which makes the interpretation of the results difficult. It is possible that an accentuated increase in ChBF in POAG patients was at least in part due to a relatively lower baseline flow level.

Comparing baseline flow levels by means of LDF technique is burdened by the different optical scattering properties of each eye. However, although individual comparisons are not allowed, comparisons between groups can be meaningful, as long as the DC values are not significantly different across the groups. This was not the case in our study cohort, and for this reason we used the DC level as a covariate in the analysis, as detailed in the Results section. In addition, an important finding, different changes in LDF flow in response to isometric exercise, is based on measurements in the same eye, expressed as a percentage.

In conclusion, baseline ChBF was reduced in untreated POAG patients and those with OHT. Mean blood pressure at baseline was reduced in the POAG group, with a comparable relative increase in the mean blood pressure during the exercise phase, ChBF increased significantly more in the glaucoma patients than in the healthy controls, indicating disturbed regulatory capacity.

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References
