Ocular Rigidity, Outflow Facility, Ocular Pulse Amplitude, and Pulsatile Ocular Blood Flow in Open-Angle Glaucoma: A Manometric Study

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Submitted: April 27, 2013
Accepted: June 5, 2013

PURPOSE. To compare ocular rigidity (OR) and outflow facility (C) coefficients in medically treated open-angle glaucoma (OAG) patients and controls, and to investigate differences in ocular pulse amplitude (OPA) and pulsatile ocular blood flow (POBF) between the two groups.

METHODS. Twenty-one OAG patients and 21 controls undergoing cataract surgery were enrolled. Patients with early or moderate primary or pseudoxfoliative OAG participated in the glaucoma group. A computer-controlled system, consisting of a pressure transducer and a microstepping device was employed intraoperatively. After cannulation of the anterior chamber, IOP was increased by infusing the eye with microvolumes of saline solution. IOP was recorded after each infusion step. At an IOP of 40 mm Hg, an IOP decay curve was recorded for 4 minutes. OR coefficients, C, OPA, and POBF were estimated from IOP and volume recordings.

RESULTS. There were no differences in age or axial length in the two groups. The OR coefficient was 0.0220 ± 0.0053 μl−1 in the OAG and 0.0222 ± 0.0039 μl−1 in the control group (P = 0.868). C was 0.092 ± 0.082 μl/min/mm Hg in the glaucoma group compared with 0.149 ± 0.085 μl/min/mm Hg in the control group at an IOP of 35 mm Hg (P < 0.001) and 0.178 ± 0.135 μl/min/mm Hg vs. 0.292 ± 0.166 μl/min/mm Hg, respectively, at an IOP of 25 mm Hg (P < 0.001). There were no differences in OPA or POBF between the two groups in baseline and increased levels of IOP (P > 0.05).

CONCLUSIONS. Manometric data reveal lower C in OAG patients and increased C with increasing IOP. There were no differences in the OR coefficient, OPA, and POBF between medically treated OAG patients and controls, failing to provide evidence of altered scleral distensibility and choroidal blood flow in OAG.

Keywords: glaucoma, biomechanics, blood flow, aqueous outflow

Increased IOP has consistently been recognized as a risk factor for the development and progression of glaucoma. Research on the parameters of aqueous humor dynamics that are altered in glaucoma has highlighted the role of impaired outflow facility as the primary pathology leading to increased IOP.1-3 Compromised outflow facility has been demonstrated in both open-angle glaucoma (OAG) patients without treatment,2 and patients with ocular hypertension.3 The available techniques of assessing aqueous humor dynamics include tonography, which was first introduced by Grant4 and fluorophotometry. Despite differences in these measurement techniques, both have enhanced our understanding of glaucoma and ocular hypertension, as well as the mechanism of action of ocular hypotensive agents.

The optic nerve head is the location of primary glaucomatous insult. It is currently recognized as a complex biomechanic structure, with IOP representing the primary mechanical load that affects neural, connective, and vascular tissues.5 Since direct experimentation is limited in the human eye, studies have looked at indirect evidence, with the use of imaging techniques and computational modeling in order to characterize the biomechanical properties of the lamina cribrosa and peripapillary sclera, and provide insight into the causal mechanisms of glaucoma. They provided evidence of the role of IOP-related stress and strain in glaucoma pathophysiology and characterized morphologic and structural parameters that affect the optic nerve head susceptibility to glaucomatous damage.6 Indeed, there is some evidence that scleral hypercompliance is observed in the early stages of glaucoma7 and it has been proposed that scleral stiffening may even prove to be protective against glaucomatous damage.8

Since measurements of scleral deformation are difficult to perform in vivo, ocular rigidity (OR) has been introduced by Friedenwald as a macroscopic parameter that measures the resistance that the eye exerts against distending forces.9 It represents the biomechanical properties of the ocular shell, including structural stiffness and geometry, mainly of the sclera. As a measure of morphologic and mechanical properties of the...
Ocular wall, changes in the OR coefficient may also reflect altered optic nerve head biomechanics in patients with glaucoma.

IOP-related stress and strain may also influence the vascular status of the optic nerve head and compromise its perfusion. The vascular theory of glaucomatous damage supported a role for vascular dysregulation at the level of the optic nerve head, leading to ischemia and reperfusion injury, in the pathogenesis of glaucoma. While the mechanical and vascular hypothesis for optic nerve head axonal damage represented different mechanisms for many years, current concepts support the close interrelation between the effects of IOP and those of optic nerve head blood flow. In healthy eyes, as well as in glaucoma and ocular hypertension patients, there is a dynamic interplay between IOP, the biomechanical properties of the ocular tissues, aqueous humor dynamics, and vascular supply.

In our previous studies, we reported measurements of OR, ocular pulse amplitude (OPA), and pulsatile ocular blood flow (POBF) in healthy human eyes. To our knowledge, there are no available data on manometric OR measurements in OAG patients in vivo. In addition, since calculations of tonographic outflow facility are influenced by the value of OR, an accurate measurement of the OR coefficient may provide better estimates of outflow facility (C). Finally, as POBF values in most studies in the literature are acquired with the use of pneumotonometry, with the assumption of a uniform OR coefficient in all eyes, assessment of the OR coefficient in every eye may provide accurate estimates of POBF in OAG patients. Therefore, in the present study, we aim to characterize the pressure-volume relation in patients with OAG and investigate whether the OR coefficient and C are altered in patients with glaucoma. This study also aims to quantify OPA and POBF and compare pulse-pressure and flow-pressure curves in treated OAG patients and controls matched for axial length.

METHODS

Patients

Patients scheduled for cataract surgery were recruited from the Ophthalmology Department, University Hospital of Larissa. The study protocol was carried out with approval from the Larissa University Hospital institutional review board. The study was in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

Twenty-one patients diagnosed with primary or pseudoexfoliation OAG and 21 controls matched for axial length were included in the study. All participants were cataract patients. One eye per patient was included in the study. Exclusion criteria for both glaucoma patients and controls were: presence of ophthalmologic disease, other than cataract and primary or pseudoexfoliation OAG, history of previous intraocular surgery, laser treatment or ocular trauma, and history of severe cardiovascular or pulmonary disease. Patients with medically treated, systemic hypertension or diabetes, without pathologic findings in dilated fundoscopy, were included in the study. Cataract patients with healthy eye exams (except from cataracts), IOP less than 22 mm Hg in at least two visits, and with no family history of glaucoma were recruited and were eligible in the control group.

All patients underwent a thorough ophthalmic assessment including slit-lamp biomicroscopy, Goldmann applanation tonometry, and dilated fundoscopy. Axial length and central corneal thickness (CCT) measurements were performed with ultrasonic biometry and pachymetry (Ocuscan; Alcon Laboratories, Inc., Irvine, CA).

Patients with early to moderate glaucoma attending the glaucoma outpatient clinic were recruited in the OAG group. The diagnosis of OAG was based on the presence of nonnocludable angles on gonioscopy, glaucomatous optic nerve appearance on dilated fundus examination, and corresponding visual field defects. All OAG patients were experienced in visual field testing and underwent visual field examination with static automated perimetry (Humphrey SITA-Standard 24-2 program; Carl Zeiss Meditec, Inc., Dublin, CA) both before surgery and at 1 month postoperatively. Presence of significant visual field defects (mean deviation smaller than −12 dB) or a vertical cup-to-disc ratio bigger than 0.9 in the preoperative evaluation were exclusion criteria for the glaucoma group.

Measurement Procedure

The measurement procedure has been explained in detail before. Briefly, a custom computer controlled device for the measurement and control of IOP was employed. This device consists of a pressure sensor (sampling rate 200 Hz, effective pressure sensitivity 0.05 mm Hg), a dosimetric syringe drive unit (volume sensitivity 0.08 µl per step), and a circuit of sterile inextensible tubes (Vygon, Ecouen, France), filled with saline solution. The measurement was controlled with custom software used for data acquisition (LabView; National Instruments, Inc., Austin, TX).

Pupil dilation was performed with phenylephrine 2.5%, tropicamide 1.0%, and cyclopentolate 1.0% drops. Topical anesthesia was applied with proparacaine and lidocaine drops and the measurement was performed under sterile conditions in the operating theatre, before cataract surgery. A standard procedure was followed both during the preparation of the system and the measurement in order to minimize the possibility of leaks or trapped air in the system. The whole measurement was performed under the operating microscope.

In every measurement, after system calibration, the anterior chamber was cannulated with a 21-gauge needle attached to the end of the tubing circuit, in order to establish free communication between the eye and the measurement device. The IOP was set to the level of 15 mm Hg with appropriate saline solution and aqueous humor exchange and was increased from 15 to 40 mm Hg, by injecting microvolumes of saline solution in the eye in a stepping procedure in all eyes. After each 4-µl infusion step, a 2-second real-time continuous recording of IOP was acquired, in order to record the rhythmic IOP oscillations with the heart beat. When the IOP reached 40 mm Hg, the infusion stopped, and the sensor continuously recorded the decreasing IOP for a period of 4 minutes.

Data Analysis and Statistics

The pressure recordings after each infusion step were analyzed and mean IOP as well as OPA, corresponding to the maximum fluctuation synchronous to the pulse rate, for each measurement window were estimated. The mean pressure (P) in each frame versus infused volume was plotted and an exponential curve was used to fit the data, based on the pressure-volume equation $P = P_0 \cdot e^{K \cdot V}$ where $P_0$ is the initial IOP, $K$ corresponds to the OR coefficient, and $V$ to volume.

A computational model was used to analyze the output data, incorporating the pressure-volume equation and the flow equation $dv/dt = -C \cdot (P - P_{ep}) - U + F$, where $F$ is the aqueous formation rate, $P$ is the instantaneous IOP, $P_{ep}$ is the episcleral venous pressure, and $U$ is the rate of uveoscleral outflow; in order to estimate $C$. An exponential curve was fitted to the pressure decay curve. Using the above equations and
subtracting the flow equation for two relatively close levels of IOP, $P_1$ and $P_2$, it can be calculated that:

$$C = \frac{dV}{dt_1} \frac{1}{kP_1} \frac{dV}{dt_2} \frac{1}{kP_2}$$

$$P_2 - P_1$$

(1)

(N. Karyotakis, et al. IOVS 2009;50 ARVO E-Abstract 808). From the latter equation, it can be seen that C changes in relation to IOP and C coefficients that correspond to an IOP of 35 mm Hg and 25 mm Hg for each patient were computed.

In order to estimate OPA, an algorithm based on the SD of the pressure readings during each 2 seconds frame was used. A low pass filter was then applied to the real time pressure signal and POBF was estimated based on a theoretical model proposed by Silver and Farrel, as the lowest value of volume flow $dV/dt$, after transforming $dP/dt$ versus time to $dV/dt$ using the individual eye's measured pressure-volume relationship. Data processing was performed with a customized software algorithm (LabView; National Instruments, Inc., Austin, TX and Matlab R2009b; Mathworks, Inc., Natick, MA). In order to approximate mean arterial pressure (MAP) from systolic (SBP) and diastolic (DBP) blood pressure measurements, the equation MAP = DBP + 0.33(SBP – DBP) was used.

Statistical analysis was performed with SPSS ver. 16 (SPSS, Inc., Chicago, IL) for Windows. Normality of distribution was assessed with the Shapiro Wilk test for each variable. Parameters are presented as either mean ± SD for variables that followed a normal distribution or as median ± inter-quartile range for skewed variables. Comparisons were performed with the unpaired $t$-test or the nonparametric Mann-Whitney $U$ test accordingly. Correlation analysis was performed with the Pearson coefficient $r$ when at least one of the tested variables followed a normal distribution and with the Spearman correlation coefficient $\rho$, if both variables were skewed. Differences in C, OPA, and POBF in different IOP levels in the same patients were evaluated with the paired samples $t$-test or the nonparametric Wilcoxon signed ranks test. The level of significance was set at 0.05.

RESULTS

Twelve primary OAG and nine pseudoexfoliative OAG patients were included in the glaucoma group. Mean age was 75.4 ± 7.8 years in the glaucoma group and 73.2 ± 5.5 years in the control group ($P=0.312$). Mean axial length was 23.24 ± 0.71 mm and 23.26 ± 0.73 mm, respectively ($P=0.931$). There was no difference in sex, systemic hemodynamics, or preoperative IOP between patients and controls. CCT was lower in the glaucoma group ($P<0.001$). Patients’ characteristics in both groups are displayed in Table 1. All glaucoma patients were under ocular hypertensive medications at the time of measurement (Table 1). There were no intra or postoperative complications related to the measurement procedure.

The OR coefficient was 0.0220 ± 0.0053 $\mu$l$^{-1}$ in the glaucoma and 0.0222 ± 0.0039 $\mu$l$^{-1}$ in the control group ($P=0.868$) (Table 2). C coefficients were lower in the glaucoma group compared with the control group, both at an IOP of 35 mm Hg (0.092 ± 0.082 vs. 0.149 ± 0.085 $\mu$l/min/mm Hg, respectively, $P<0.001$), and at an IOP of 25 mm Hg (0.178 ± 0.135 vs. 0.292 ± 0.166 $\mu$l/min/mm Hg, respectively, $P<0.001$). C coefficients at an IOP of 35 mm Hg were lower than C at 25 mm Hg in all eyes ($P<0.001$). There was no correlation between the OR coefficient and C at 35 mm Hg ($r=0.073$, $P=0.647$) or at 25 mm Hg ($r=-0.08$, $P=0.613$). When the quotients of C at an IOP of 35 mm Hg and C at 25 mm Hg were compared between patients and controls, no difference was found ($P=0.497$).

Baseline OPA was 2.51 ± 1.04 mm Hg in the glaucoma group and increased by 0.078 ± 0.040 mm Hg/mm Hg change in IOP ($P<0.001$), with increasing IOP from 15 to 40 mm Hg. OPA was 2.26 ± 0.63 mm Hg in the control group and increased by 0.068 ± 0.043 mm Hg/mm Hg change in IOP ($P<0.001$), with increasing IOP from 15 to 40 mm Hg. When OPA values were compared, no difference was observed in baseline (15 mm Hg) or elevated (40 mm Hg) IOP between the two groups, as shown in Table 2.

To evaluate differences in blood flow, POBF values were grouped in five IOP levels. POBF was 1055 ± 271 $\mu$l/min in the glaucoma and 962 ± 255 $\mu$l/min in the control group, at baseline, decreasing by 32.8 ± 8.2% ($P<0.001$) and 29.5 ± 11.8% ($P<0.001$), respectively, with increasing IOP from 15 to 40 mm Hg. Comparisons between patients and controls in all five IOP levels revealed no difference between the two groups (Table 2). No difference was found in the percentage decrease in POBF from baseline to elevated IOP between patients and controls ($P=0.302$). There was no correlation between POBF in baseline and elevated IOP and MAP in either group (Spearman correlation test, $P>0.200$ for all comparisons).

DISCUSSION

In the present study, differences in OR, outflow facility, and ocular hemodynamic parameters, including OPA and POBF, were investigated between OAG glaucoma patients and controls scheduled for cataract surgery. While OAG patients exhibit lower C, the OR coefficient was not statistically different between the two groups. Additionally, OPA and POBF were not found to differ in OAG patients and controls.

There has been long standing discussion about the role of biomechanics in the pathogenesis of glaucoma. The hypothesis of the present study was that scleral distensibility may be altered in OAG. Scleral biomechanics may be implicated in the pathophysiology of glaucoma in two ways: firstly, certain scleral material properties may be involved in glaucoma susceptibility in different levels of IOP, and secondly, they may be altered as a consequence of prolonged exposure to increased IOP. In this context, changes in the scleral properties detected in monkey eyes subjected to elevated IOP include stiffening, which may be preceded by scleral hypercompliance in some eyes, and these changes are believed to reflect remodeling of the scleral extracellular matrix. In addition, finite element modeling studies have shown that scleral properties strongly influence the biomechanic behavior of the optic nerve head and may constitute a risk factor for glaucoma. However, ex vivo inflation testing experiments performed in human donor eyes, while showing meridional stiffening in the peripapillary region, provide no evidence of differences in the stress-strain response in the midposterior sclera, suggesting that the changes occurring in glaucoma are localized in the peripapillary tissues.

Changes in OR in glaucoma patients were firstly investigated by Friedenwald with the use of paired Schiotz tonometry. He reported that untreated glaucoma patients exhibit increased values of the OR coefficient, which normalize upon institution of medical or surgical IOP lowering therapy. An increase in the OR coefficient after prolonged IOP increase has also been documented in animal studies (in rabbits). Since Friedenwald’s method uses only two pressure volume data pairs, the higher OR values in patients with high IOP could be, at least in part, confounded by the dependence of the OR coefficient on IOP. In the present study, the same range of IOPs was used in both patients and controls to estimate the OR coefficient in order to directly compare the data between the two groups.
In this study, to our knowledge, the first to report both OR and C coefficients in OAG patients, measured with an accurate, yet invasive, intraoperative method. In fact, the two groups in the present study were matched for axial length since it is the primary factor that has consistently been associated with the OR coefficient. Age has been proposed as another factor that influences the OR coefficient. A decrease in C with age has also been reported in some, but not all studies. Again, the two groups did not differ in age. Finally, the preoperative IOP was also the same in patients and controls, due to pharmacologic treatment, allowing for direct comparisons in the outcome variables between the groups.

It is generally accepted in the literature that C is not influenced by IOP. However, the finding of lower C in higher IOPs is not new, based on experimental data on animal models and postmortem human eyes. In fact, in the present study, C decreased with increasing IOP in all eyes tested. The relation of C to IOP may reflect changes in the anterior chamber depth, alterations in angle configuration or Schlemm’s canal collapse during the measurement.

Table 1. Baseline Characteristics in the Glaucoma and Control Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glaucoma Group, N = 21</th>
<th>Control Group, N = 21</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75.4 ± 7.8</td>
<td>73.2 ± 5.5</td>
<td>0.312*</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>10/11</td>
<td>12/9</td>
<td>0.575†</td>
</tr>
<tr>
<td>Right/left eye</td>
<td>9/12</td>
<td>8/13</td>
<td>0.528†</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>25.24 ± 0.71</td>
<td>25.26 ± 0.73</td>
<td>0.931*</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>514 ± 23</td>
<td>541 ± 23</td>
<td>0.001†</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>96.0 ± 12.7</td>
<td>97.3 ± 27.5</td>
<td>0.57†</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>71 ± 18</td>
<td>65 ± 18</td>
<td>0.074†</td>
</tr>
<tr>
<td>Preoperative IOP, mm Hg</td>
<td>16.0 ± 5.0</td>
<td>14.5 ± 4.8</td>
<td>0.365†</td>
</tr>
<tr>
<td>Vertical cup/disc ratio</td>
<td>0.60 ± 0.13</td>
<td>0.27 ± 0.11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean deviation, dB</td>
<td>−3.78 ± 2.58</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Topical medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latanoprost</td>
<td>9</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>1</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>1</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>1</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>2</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Dorzolamide-timolol</td>
<td>7</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Brimonidine</td>
<td>3</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Latanoprost-timolol</td>
<td>1</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Bimatoprost-timolol</td>
<td>4</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SD and comparisons are made with the unpaired t-test.
† Data are presented as median ± interquartile range and comparisons are performed with the Mann-Whitney U test.

Hommer et al. employed a different approach and reported higher values of an OR parameter, computed as the product of OPA measured with pneumotonomometry and fundus pulsation amplitude assessed with laser interferometry, suggesting decreased compliance in treated primary OAG patients compared to controls. In another study, Ebner used another metric for OR, that included OPA with dynamic contour tonometry and the change in axial length induced by IOP lowering with acetazolamide measured with partial coherence laser interferometry. They again reported increased values of this parameter in treated glaucoma patients. Wang et al. used another measure of OR, employing OPA with dynamic contour tonometry and pulsatile choroidal blood flow assessed with laser Doppler flowmetry. In that study, patients with OAG were reported to exhibit lower values of this parameter and ocular hypertensives higher values compared with controls. However, it is important to acknowledge that a direct comparison between the above cited studies and the present study were medical records of patients and controls, due to pharmacologic treatment, allowing for direct comparisons in the outcome variables between the groups.

Table 2. Measured Parameters in the Glaucoma and Control Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glaucoma Group, N = 21</th>
<th>Control Group, N = 21</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigid coefficient, 1/μL</td>
<td>0.0220 ± 0.0053</td>
<td>0.0222 ± 0.0039</td>
<td>0.868*</td>
</tr>
<tr>
<td>Outflow coefficient at 35 mm Hg, μL/min/mm Hg</td>
<td>0.092 ± 0.082</td>
<td>0.149 ± 0.085</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Outflow coefficient at 25 mm Hg, μL/min/mm Hg</td>
<td>0.178 ± 0.135</td>
<td>0.292 ± 0.166</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>OPA at 15 mm Hg</td>
<td>2.51 ± 1.04</td>
<td>2.26 ± 0.63</td>
<td>0.362*</td>
</tr>
<tr>
<td>OPA at 40 mm Hg</td>
<td>4.04 ± 1.34</td>
<td>4.04 ± 1.34</td>
<td>0.568*</td>
</tr>
<tr>
<td>POFB at 15–20 mm Hg, μL/min</td>
<td>1055 ± 271</td>
<td>962 ± 255</td>
<td>0.258*</td>
</tr>
<tr>
<td>POFB at 20–25 mm Hg, μL/min</td>
<td>848 ± 357</td>
<td>870 ± 322</td>
<td>0.359†</td>
</tr>
<tr>
<td>POFB at 25–30 mm Hg, μL/min</td>
<td>782 ± 335</td>
<td>721 ± 382</td>
<td>0.589†</td>
</tr>
<tr>
<td>POFB at 30–35 mm Hg, μL/min</td>
<td>682 ± 372</td>
<td>662 ± 315</td>
<td>0.587†</td>
</tr>
<tr>
<td>POFB at 35–40 mm Hg, μL/min</td>
<td>679 ± 258</td>
<td>610 ± 270</td>
<td>0.419†</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SD and comparisons are made with the unpaired t-test.
† Data are presented as median ± interquartile range and comparisons are performed with the Mann-Whitney U test.
Decreased outflow facility is the primary mechanism leading to ocular hypertension. It results from outflow obstruction due to the accumulation of extracellular material in both the trabecular meshwork and ciliary muscle, and a loss of trabecular meshwork cells. Larsson et al. reported lower outflow facility in untreated OAG patients compared with age-matched controls. This difference in outflow resistance is also evident in our study in OAG patients, despite antiglaucoma treatment. Our measurements are generally in agreement with values for C reported by Larsson et al. Fluorophotometric outflow facility values, being independent of OR and pseudofacility, are slightly different, but differences between patients with ocular hypertension and controls have again been demonstrated with this technique. In the present study, we employed the increased level of IOP reached at the end of the OR measurement to record an IOP decay curve. To quantify the outflow resistance, processing algorithms that incorporated the OR coefficient were used, in order to minimize errors in the calculations due to OR.

All measurements were conducted while the patients were receiving their glaucoma treatment, since it would be unethical to wash out and submit them to surgery without medications. They were all pharmacologically treated and had not been submitted to trabecuoplasty or filtering procedures. In addition, none of the patients enrolled were on parasympathomimetics, which would address the pathology of impaired outflow facility. The majority of our patients (71%) were indeed receiving prostaglandins, which have been associated with increased outflow through the uveoscleral pathway, while they have been shown to enhance trabecular outflow facility as well in some studies. However, no difference in outflow facility was found in a crossover study in ocular hypertensives comparing no treatment and therapy with latanoprost, timolol maleate, and dorzolamide. Moreover, beta blockers, alpha agonists, and carbonic anhydrase inhibitors work mainly by aqueous flow suppression, while alpha agonists also increase the uveoscleral outflow. However, since the algorithms used in the present study provide estimates for C relatively independent of values for F, U, and P_{ep}, differences in the method of action between hypotensive agents should not introduce large errors in our calculations.

Another result of the present study was the increase in OPA with increasing IOP, which was uniform in both groups and agrees with reports from a previous investigation in healthy eyes. In addition, a well proven dependence of OPA with increasing IOP, which was a uniform finding in both groups. However, in untreated POAG, normal-tension glaucoma, and controls, no difference in POBF was detected. Hence, the purpose of this study was to provide initial evidence of possible differences in these parameters, rather than address these important questions with an invasive manometric procedure.

Furthermore, the dynamic character of the measurement technique used cannot exclude an effect of the measurement on the measured parameters, and especially POBF as a result of IOP lowering in the beginning of the procedure. Between subjects differences in blood flow response to changes in IOP may also ensue. The large variability of POBF values that has also been described previously with the use of noninvasive techniques in both groups was also evident in the results of the present study.

Moreover, in order to estimate POBF, the algorithms proposed by Silver et al. were used and the assumptions inherent in the calculations were adopted. Furthermore, it remains unknown whether the same pressure volume relation as measured with our microstepping technique also applies to the IOP oscillations due to the pulsatile inflow of blood in the choroid. Finally, as previously mentioned, these results may be confounded by the pharmacologic intervention in OAG patients, which on the other hand can allow direct comparisons between the groups in the same IOP levels.
In conclusion, OAG patients exhibit lower outflow facility coefficients, compared with controls, whereas no difference was found in the OR coefficient, OPA, and POBF in baseline and increased IOP. This study can serve as a point of reference for future large scale studies employing less invasive techniques to quantify these parameters and may provide insight into the causal mechanisms of OAG.

Acknowledgments

Disclosure: A.I. Dastiridou, None; E.E. Tsironi, None; M.K. Tsilimbaris, None; H. Ginis, None; N. Karyotakis, None; P. Cholevas, None; S. Androudi, None; I.G. Pallikaris, None

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