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CLINICAL STUDY

Non-invasive biometric assessment of ocular rigidity in glaucoma patients and controls

A Ebneter, B Wagels and MS Zinkernagel

Abstract

Purpose **To determine *in vivo* whether a pharmacologically induced change in intraocular pressure (IOP) leads to measurable changes in axial eye length and whether there is a difference between glaucoma patients and control subjects.**

Methods **42 subjects (19 patients with primary open angle glaucoma and 23 control patients matched for age and gender) underwent axial eye length measurement using partial coherence laser interferometry and measurement of IOP using dynamic contour tonometry before and 2 h after oral intake of 500 mg acetazolamide. Student's *t*-test was used to compare differences in the means.**

Results **An identical drop in IOP was induced in both the glaucoma (mean ± SEM: 2.90 ± 0.44 mmHg, $n = 19$) and the control group (mean ± SEM: 3.17 ± 0.32 mmHg, $n = 23$). The change in axial eye length was significantly smaller ($P = 0.026$) in the glaucoma group (mean ± SEM: −14.2 ± 3.2 μm, $n = 19$) compared with the control group (mean ± SEM: −23.0 ± 2.98 μm, $n = 23$).**

Conclusions **Our results strongly suggest that the ocular rigidity is increased in patients with established glaucoma in comparison to control subjects. Ocular rigidity could play a role in the pathogenesis and pathophysiology of glaucoma. Determination of ocular rigidity could be helpful in detection of glaucoma.**

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Keywords: ocular rigidity; axial eye length; primary open angle glaucoma; partial coherence laser interferometry

Department of Ophthalmology, Cantonal Hospital St Gallen, St Gallen, Switzerland

Correspondence:
Dr med A Ebneter,
Augenklinik Kantonsspital,
Rorschacherstrasse 95,
St Gallen,
CH—9007,
Switzerland
Tel: +41 71 494 17 71;
Fax: +41 71 494 28 81.
E-mail: ebneter.andreas@gmail.com

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Introduction

Ocular rigidity is a biomechanical parameter of the eye expressing the elasticity of the globe. It depends mainly on the properties of the cornea, sclera and other components of the outer shell of the eye. Ocular rigidity relates intraocular pressure changes to the corresponding volume changes and is a measure of the resistance that the eye exerts to distending forces.[1] Probably the most commonly used pressure–volume relationship is that developed by Friedenwald.[2] This formula is based on measurements performed on cadaver eyes. A more sophisticated model has been proposed by Silver *et al*.[3] This group derived the pressure–volume relation by numerical experimentation using all previously published rigidity measurements on living human eyes. The formula took the form $\Delta V = V \times (C + C_0 \times \ln P + C_1 \times P)$. ΔV is the increment of volume over an arbitrary reference volume. V is the volume of the eye. P is the intraocular pressure. The numerical parameters C ($= -8.03 \times 10^{-3}$), C_0 ($= 4.87 \times 10^{-3}$) and C_1 ($= 3.90 \times 10^{-5}\,mmHg^{-1}$) have been determined by least-square fitting of a polynomial function to the rigidity measurements.

Ocular rigidity is influenced by many factors. Marked differences were seen when the ocular rigidity measured on living eyes was compared with the ocular rigidity measured on the same eyes after enucleation. Ocular rigidity of enucleated eyes is higher than that in living human eyes. The difference seems to arise from choroidal blood flow.[4–6] It is therefore essential to perform *in vivo* measurements. Ocular rigidity is inversely proportional to the eye volume.[7] In myopic eyes rigidity is decreased, whereas in hyperopic eyes it is increased. On the other hand, ocular rigidity is directly

proportional to intraocular pressure.[6,8] In a higher pressure state, it is more elevated than in a lower pressure state. A recent study by Pallikaris *et al*[9] showed a positive correlation between the ocular rigidity coefficient and age. Ocular rigidity seems to be altered in long-standing glaucoma.[10] There is an ongoing debate on the role of ocular rigidity in the pathogenesis of myopia and age-related macular degeneration. Although several studies evaluated these topics, results remain controversial.[11–13]

An established way of measuring ocular rigidity in living eyes is by injecting small-volume increments into the anterior chamber and measuring the resulting pressure change.[9] However, this is an invasive method and not suitable for everyday clinical practice. Furthermore, concerns have been raised regarding accuracy of this method because of the valve effect of the iris–lens diaphragm.[14,15]

The intraocular volume and its changes are not directly measurable by simple means. However, axial length certainly contributes to the overall size of the eye and may even be the determining factor. Consequently, changes in axial length due to intraocular pressure (IOP) changes should be influenced by ocular rigidity. Axial length can easily and precisely be measured.[16–18] Several studies have shown a decrease of axial eye length with lowered intraocular pressure after trabeculectomy.[19–22] A recent study by Leydolt *et al*[23] measured the change of axial eye length after mechanically inducing intraocular pressure elevation.

The aim of this study was to investigate the effect of pharmacologically induced short-term IOP lowering on the axial length in emmetropic eyes and to assess differences between eyes with primary open-angle glaucoma and healthy eyes.

Materials and methods

The study was performed according to the tenets of the Declaration of Helsinki and approved by the ethics committee of the Canton of St Gallen. Informed consent was obtained from all subjects in this study after the nature and possible consequences of the study had been explained. Before inclusion, each subject passed an ophthalmic evaluation consisting of a medical history, a slit lamp examination and a biomicroscopic inspection of the optic disc and the central retina.

Inclusion criteria for patients with glaucoma were a repeatable abnormal visual field in the examination program G2 (Cupola Perimeter Octopus 101, Haag Streit, Köniz, Switzerland) and at least two documented IOP measurements of >22 mmHg. Healthy eyes were defined as those with healthy-appearing optic discs on biomicroscopic examination and no history of IOP >22 mmHg. Exclusion criteria in both groups included any contraindication to the use of acetazolamide, any previous incisional surgery, narrow angle in gonioscopy, any form of secondary glaucoma, corneal anomalies, myopia of more than -2.0 diopters spherical equivalent or hyperopia of more than $+1.0$ diopter spherical equivalent.

We included 42 eyes of 42 subjects in this prospective comparative clinical trial. Control subjects were matched for gender and age to within 5 years. Only one eye per subject was included. In the control group, we always considered the right eye. In the glaucoma group, we primarily included the eye fulfilling the inclusion criteria. If both eyes qualified, we included the one showing more advanced glaucomatous damage in terms of visual field changes.

Axial eye length, defined as the distance from the anterior corneal surface to the retinal pigment epithelium along the visual axis using a red fixation beam, was measured with the commercially available IOL Master (Zeiss Meditec, Jena, Germany) using partial coherence laser interferometry. In measuring axial eye length, the IOL Master is reported to have a resolution of about 10 μm and a precision of 5 μm.[24] Five single measurements were obtained for each eye through an undilated pupil with the patient in a sitting position. The mean was calculated by the IOL Master. Axial eye length was always measured before IOP.

Intraocular pressure measurements were obtained by using dynamic contour tonometry (PASCAL Dynamic Contour Tonometer, Ziemer Ophthalmic Systems AG, Port, Switzerland). The influence of central corneal thickness and other corneal parameters on IOP readings are minimized using this method.[25] Before each measurement, one drop of proxymetacaine (Alcaine, Alcon, Switzerland) was instilled into the conjunctival sac for local anaesthesia. Only records with a good-quality index (Q1 or Q2) were taken into account.

Intraocular pressure was decreased pharmacologically by 500 mg acetazolamide. Baseline measurements of axial eye length, IOP, blood pressure and arterial pulse were taken at the beginning of the examination. Thereafter, two tablets of Diamox (250 mg) were swallowed by the examinee in the presence of the examiner. Axial length, IOP, blood pressure and arterial pulse were measured again 2 h later. It has previously been shown that maximal IOP lowering is reached 2 h after oral administration.[26] Finally, central corneal thickness was assessed using ultrasonic pachymetry (300P Pacscan Pachymeter, Sonomed Inc., Lake Success, NY, USA).

Throughout the text, data are presented as mean value ± SEM. The Student's *t*-tests for independent samples was used to compare the means, considering $P<0.05$ for statistical significance. Statistical analysis was

Table 1 Baseline characteristics and induced IOP change

Characteristic	*Glaucoma group* (n = *19*)	*Control subjects* (n = *23*)	P-*value* (t-*test*)
Male subjects (number)	8 (42%)	11 (48%)	0.719
Age (years)	64.6 (61.4–67.8)	64.5 (61.9–67.1)	0.955
Axial length (mm)	23.70 (23.10–24.30)	23.57 (23.14–24.00)	0.701
Corneal thickness (μm)	546 (527–564)	542 (527–556)	0.717
Initial IOP (mmHg)	18.3 (17.1–19.6)	16.2 (15.1–17.3)	0.009
IOP drop (mmHg)	2.9 (2.0–3.8)	3.2 (2.5–3.8)	0.611
IOP drop (%)	15.8 (10.6–21.0)	19.2 (16.0–22.4)	0.238

Except for gender, data are presented as mean value and 95% confidence interval.

performed with Prism 4 for Windows (GraphPad Software Inc., San Diego, CA, USA).

Results

Nineteen eyes suffering from primary open-angle glaucoma were included in the glaucoma group ($n = 19$, mean age 64.6 years, range 52–74). The control group consisted of 23 healthy eyes ($n = 23$, mean age 64.5 years, range 54–76). Except for initial IOP, the baseline characteristics in the two groups were identical (Table 1). Acetazolamide led to an identical drop of IOP in both groups ($P = 0.61$) 2 h after oral intake. In the glaucomatous eyes, the IOP fell by 2.90 ± 0.44 mmHg (mean ± SEM, $n = 19$), corresponding to a 16% reduction. In the control subjects, the intraocular pressure diminished by 3.17 ± 0.32 mmHg (mean ± SEM, $n = 23$) or 19%, respectively. Relative pressure lowering in both groups was not statistically different ($P = 0.24$).

In the glaucoma group, the axial length decreased by 14 ± 3.3 μm (mean ± SEM, $n = 19$). This decrease is highly statistically significant at a level of $P = 0.0004$. In the control population, axial length diminished by 23 ± 3.0 μm (mean ± SEM, $n = 23$) at an even more significant level ($P < 0.0001$). In addition, the change in axial length induced by identical lowering of IOP was significantly different between the two groups with $P = 0.026$ (Figure 1). Mean axial eye length shortening per mmHg of IOP decrease was also calculated and was found to be 5.2 ± 1.5 μm/mmHg (mean ± SEM, $n = 19$) in glaucoma eyes and 9.1 ± 1.6 μm/mmHg (mean ± SEM, $n = 23$) in the healthy ones. This difference was also statistically significant ($P = 0.047$).

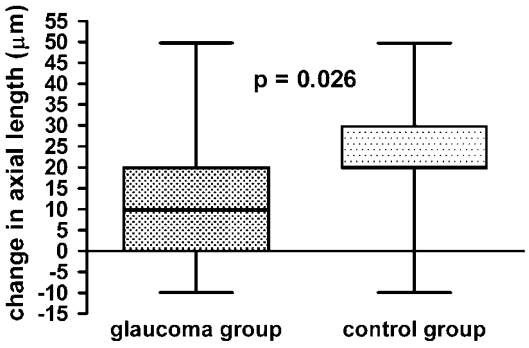

Figure 1 Axial eye length change induced by identical IOP lowering.

Discussion

With pharmacologically induced short-term lowering of IOP after systemic administration of acetazolamide, we found a significant shortening in axial eye length. A decrease in axial eye length due to lowered intraocular pressure has been shown in several previous studies[19–23] To our knowledge, this is the first study to demonstrate this effect after systemic administration of acetazolamide and the first to investigate the difference in rigidity between healthy and glaucomatous eyes *in vivo*. The resulting axial eye length decrease per mmHg IOP reduction was smaller for the glaucomatous eyes than for the healthy ones, suggesting that glaucomatous eyes are more rigid. The intraocular volume change resulting from a certain amount of IOP change is dependent on the eyeball's rigidity. In a condition with elevated rigidity, an identical decrease in distending forces would induce a smaller change in dimensions than in a normal eye.

There are several advantages of our method compared with previous studies. Leydolt *et al*[23] used a suction cup causing mechanical stress and local deformation to the sclera to induce IOP changes. Use of the suction cup could cause deformation of the entire globe, resulting in axial eye length alterations independent of pressure change. We obtained IOP lowering by pharmacological means only without manipulation of the bulbus. We did all the examinations and measurements with undilated pupils.

However, the changes in axial length obtained using acetazolamide were small and very close to the resolution limit of the currently available machines using partial coherence interferometry. Furthermore, it is unknown if there is an effect of acetazolamide on the thickness of the choroid and on scleral rigidity.

Table 2 Literature overview on pressure-induced axial eye length change

Author	*Year*	*Eyes*	*Setting*	*Method*	*Time after pressure lowering or surgery* *Axial length change per mmHg (μm/mmHg)*				
Leydolt *et al*[23]	2007	18	Suction cup technique	IOL Master			Immediate 2		
Kiss B *et al* ARVO Abstract 2379	1999	NA	Timolol 0.5%	Laser interferometer			Hours 6,5		
Francis BA *et al*[22]	2005	39	Trabeculectomy	IOL Master	1 week 20.0		1 month 15.6		>3 months 3.9
Francis BA *et al*[22]	2005	22	Glaucoma drainage device	IOL Master	1 week 13.5		1 month 38.0		>3 months 12.1
Kook *et al*[20]	2000	18	Trabeculectomy	A-scan biometry	1 week 21.9	1 month 22.1	3 months 20.2	6 months 19.3	12 months 19.1
Cashwell *et al*[19]	1999	18	Glaucoma filtering surgery	A-scan biometry			22 months 25.6		

The observed changes in axial eye length are comparable to existing data already published (Table 2). Leydolt *et al*[23] observed changes in axial eye length using the IOL Master in healthy eyes similar to our measurements. This highly precise non-contact technique based on partial laser interferometry was also used by Francis *et al*[22] to evaluate axial eye length shortening after glaucoma surgery. Changes turned out to be more pronounced, especially in the early course after surgery. However, the setting was different in that pressure was measured in the long-term course and the structural integrity of the bulbus might be considerably altered by filtering surgery. Three months after surgery, the axial eye length change per mmHg of pressure decrease was again quite close to our values. The relationship between ocular rigidity and IOP is likely not linear and there might be a threshold of IOP reduction below which significant axial eye length reduction results. In the study by Francis *et al*, the axial eye length decrease was significantly more important in hypotonous eyes. We guess that normal eyes might even be more prone to considerable length decrease after profound IOP reduction due to lower rigidity. Farther back, Kook *et al*[20] and Cashwell *et al*[19] studied axial eye length changes after filtering glaucoma surgery. In the long-term course (12–22 months), they found shortening of the bulbus of about 20–25 μm/mmHg. This is about twice the changes noted by Francis *et al*[22] in a comparable setting. This difference might be due to the fact that A-scan biometry was used by Kook *et al*. This ultrasound-based method requires direct contact to the cornea during measurement and is likely to induce bias, especially in hypotonous eyes. Moreover, resolution and precision of partial coherence interferometry is known to be about 10 times better than that of ultrasound-based methods.[16,24]

Recent studies using finite element modelling showed that the biomechanical properties of the corneoscleral shell profoundly affect the level of mechanical stress experienced by the optic nerve head (ONH).[27,28] Forces at the ONH have been shown to be up to 180 times IOP.[29] Several previous studies found ocular rigidity to be increased in glaucomatous eyes. We hypothesize that this might be due to structural changes of the sclera. Tengroth *et al*[30] found changes in the content and composition of collagen fibres in the eyes of glaucoma patients. Moreover, the prevalence of glaucoma augments with age.[31] With aging, the connective tissue becomes more rigid due to an increase in the cross-sectional area of the fibrils and an increase in cross-linking.[32] Thus, to a certain extent, increased rigidity can be seen as a part of the normal aging process.[2] A very recent nutritional study points to the potential importance of dietary habits. Nguyen *et al*[33] found both decreased IOP and decreased rigidity in the eyes of rats on an omega-3 polyunsaturated fatty acids-sufficient diet compared with animals on an omega-3 fatty acids-deficient diet.

The question whether the biomechanical changes are a consequence or part of the pathogenesis of the disease is much more delicate. There is pretty good evidence that ocular rigidity is increased in established glaucoma cases. But it might be possible that ocular rigidity changes in the course of the disease. Drance[10] postulated decreased scleral rigidity in untreated glaucoma patients. Agrawal *et al*[34] found that decreased scleral rigidity rose to almost normal values after topical treatment with timolol or pilocarpine. Downs *et al*[35] noticed increased peripapillary rigidity in monkey eyes in early experimental glaucoma. In our cross-sectional study, the diagnosis of glaucoma was well established, most patients had topical pressure-lowering treatment and all showed signs of axonal damage. To address the issue at which stage of the disease increased ocular rigidity becomes manifest, longitudinal studies would be necessary.

In summary, we were able to show different *in vivo* changes in axial eye length after medically induced IOP

lowering in patients with open-angle glaucoma compared to matched control patients. Our results suggest that ocular rigidity might be increased in eyes with primary open-angle glaucoma. Our non-invasive method for indirect measurement of ocular rigidity might be an additional tool for the diagnosis of glaucoma and shed new light on the pathogenesis of this common eye disease. However, to confirm our findings and verify methodical accuracy, further studies with larger numbers of patients and preferably more precise measurement of axial eye length will be needed. Accurate, simple and non-invasive methods for measuring ocular rigidity would make future investigations more effective and faster.

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Declared financial interests

Ziemer Ophthalmic Systems AG (Port, Switzerland) offered us a PASCAL Dynamic Contour Tonometer at a reduced rate to conduct this study.

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