

Estimation of Ocular Rigidity in Glaucoma Using Ocular Pulse Amplitude and Pulsatile Choroidal Blood Flow

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PURPOSE. Theoretical models and animal studies have suggested that scleral rigidity plays an important role in the pathogenesis of glaucoma. The aim of this study was to present a noninvasive technique for estimating ocular rigidity (E) in vivo, and to compare the estimated rigidity between patients with open-angle glaucoma (OAG); ocular hypertension (OHT); suspect glaucomatous disc (GS); and normal subjects (N). We hypothesized that OHT patients would have higher rigidity.

METHODS. All patients underwent measurements of ocular pulse amplitude (OPA) using dynamic contour tonometry, pulsatile choroidal blood flow (ChBF_p) using laser Doppler flowmetry; axial length (AL); and assessment of automated visual field mean deviation (MD). The ratio between OPA and ChBF_p was calculated according to the Friedenwald's equation of ocular rigidity. The calculated ratio is denoted as (E_R). The average E_R values of the four diagnostic groups were compared using nonparametric tests. The relationship between E_R and other ocular and systemic factors was examined using correlation and regression analysis.

RESULTS. A total of 257 subjects were included in the study (56 N, 108 OAG, 48 GS, and 45 OHT). E_R correlated negatively with AL and positively with MD, signifying that a lower rigidity was associated with a longer eye and a worse (more negative) MD. E_R was also found to be highest in OHT (0.235 ± 0.16) and lowest in OAG (0.188 ± 0.14 ; $P = 0.01$).

CONCLUSIONS. Estimated coefficient of ocular rigidity by OPA and ChBF_p suggested that glaucoma patients had the lowest rigidity and OHT the highest. It supports the idea that a more compliant ocular shell may predispose the optic nerve head to intraocular pressure (IOP)-related damage. (*Invest Ophthalmol Vis Sci.* 2013;54:1706-1711) DOI:10.1167/iovs.12-9841

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Studies of human cadaver eyes, animal studies, and theoretical models of optic nerve head stresses and strains have suggested that scleral rigidity may play a role in the pathogenesis of open-angle glaucoma. Based on theoretical models, it has been hypothesized that decreased scleral stiffness (decreased rigidity) was associated with more deformation (strain) of the lamina cribrosa (LC) and subsequently more axonal damage in the presence of high intraocular pressure (IOP).¹ Therefore, scleral stiffness could be a determinant for individual optic nerve head susceptibility to the damage caused by elevated IOP.

The stiffness of sclera (a real material property) is difficult to evaluate in vivo. An alternative is to measure ocular rigidity, which is the term used to describe the relationship between pressure and volume changes in the eye. Friedenwald has defined ocular rigidity as a measure of the resistance that the eyeball offered to a change in intraocular pressure. Ocular rigidity is therefore a combined structural stiffness of the sclera, choroidal vascular bed, retina, and cornea. The coefficient of ocular rigidity (E) is described by the Friedenwald equation²:

$$E = (\log IOP_1 - \log IOP_2) / (V_1 - V_2), \quad (1)$$

where the slope of the log-transformed pressure-volume relationship of the eye ($\Delta IOP / \Delta V$) is the coefficient of ocular rigidity (E). A higher E value signifies that the eye is stiffer with a consequent larger increase in pressure (IOP) as volume (V) increases; a lower E signifies a less stiff eye with a smaller increase in pressure as volume increases.

Both invasive and noninvasive methods of estimating E have been described in the literature. The invasive method involves injecting a known volume of liquid into the eye (ΔV) and measuring the subsequent increase of IOP (ΔIOP); the curve of pressure-volume relationship is plotted and the coefficient of rigidity (E) is calculated based on the Friedenwald's equation.^{3,4} The noninvasive method benefits from the fact that each cardiac cycle brings a bolus of blood into the ocular circulation. This inflow of blood (ΔV) subsequently increases the IOP (ΔIOP), which is called ocular pulse amplitude (OPA) or pulse amplitude (PA). OPA can be easily measured with a pneumotonometer or a dynamic contour tonometry. The difficulty in a noninvasive method of estimating ocular rigidity is in the estimation of ΔV , which is mostly the result of the pulsatile component of choroidal blood flow.⁵ In the article by Hommer et al., they used fundus pulse amplitude (FPA) as ΔV , which measures the movement between the cornea and inner retina in response to the cardiac pulse.⁶ Ebnetter et al. pharmacologically reduced IOP using acetazolamide (ΔIOP) and measured the change in axial length following the reduction of IOP (ΔV).⁷ They compared the amount of reduction in axial length (AL) between individuals who have achieved the same amount of IOP reduction; individuals with greater AL reduction were considered as having lower rigidity.

Both noninvasive methods, using either FPA or AL, estimated ΔV by measuring the anterior to posterior expansion of the corneoscleral shell, which is itself dependent on the ocular rigidity, the preexisting volume of the choroidal circulation, and the preexisting IOP level.⁸ It may, therefore, be more pertinent to use a variable that indicates the amount of blood injected into the eye with each cardiac cycle as an indicator of ΔV rather than a variable indicating the response of ocular coat to an increase in volume.

The increase in ocular volume associated with each cardiac pulse (ΔV) is predominantly the pulsatile component of choroidal circulation.⁵ It can be measured noninvasively by one of the three instruments: the Langham ocular blood flow system, laser interferometry, or subfoveal laser Doppler flowmetry. All three methods have their own limitation. The Langham ocular blood flow system, using a pneumotometry interfaced with a microcomputer, measures the pulse amplitude (i.e., OPA) and derives from it the pulsatile ocular blood flow (POBF) assuming a constant rigidity for each eye. Since the ocular rigidity varies between eyes, POBF is not an accurate indicator of ΔV .^{7,8} Laser interferometry measures FPA, as previously mentioned, which is the expansion of the distance between the cornea and inner retina with each cardiac pulse.⁹ The inward expansion of the inner retina is likely the result of choroidal filling with each cardiac pulse. The limitation of using FPA as ΔV is that the cornea, and probably the posterior sclera, also move significantly outward with each pulse, and these movements depend on the rigidity of corneoscleral coat.¹⁰ Therefore, using FPA as ΔV is also biased by ocular rigidity.

Subfoveal laser Doppler flowmetry (LDF) measures the movement of red blood cells based on the Doppler principles.¹¹ Due to the lack of retinal vessel in the subfoveal region, the movement of red blood cells detected by LDF is of choroidal origin. LDF provides three choroidal blood flow parameters: choroidal blood velocity (ChBVel) in units of Hz; choroidal blood volume (ChBVol) in arbitrary units (AU); and choroidal blood flow (ChBF) in AU. The three parameters are related to each other through the equation: $\text{ChBF} = k \times \text{ChBVel} \times \text{ChBVol}$, where k is a proportionality constant. LDF measures the subfoveal choroidal blood flow continuously and detects in this flow the cardiac pulse. Therefore, both systolic and diastolic values of the three variables are measured, and the mean and the pulsatility (the difference between the systolic and diastolic values) of each variable are calculated. The mean values of ChBVel, ChBVol, and ChBF are reported by most of studies in the subject of subfoveal blood flow. They are decreased in myopic patients, in patients with high IOP, in glaucoma patients, and in patients with age-related macular degeneration.¹² The mean ChBF also demonstrates autoregulatory capacity within a certain range of blood pressure; it is maintained when the ocular perfusion pressure (OPP) is decreased through the manipulation of IOP or blood pressure.^{12,13} The pulsatile choroidal blood flow (ChBF_p) is calculated by LDF as the following: $\text{ChBF}_p = (\text{systolic ChBF} - \text{diastolic ChBF})/\text{systolic ChBF}$.

The mean ChBF reflects both the steady and pulsatile components of choroidal circulation whereas ChBF_p reflects solely the pulsatile component. ChBF_p is less well-studied than the mean ChBF. In the article published by Riva et al., ChBF_p is influenced by the perfusion pressure (i.e., both blood pressure and IOP).¹³

Among the three estimates of pulsatile choroidal blood flow (ΔV), POBF and FPA reflect the pulsatile blood flow of the entire choroidal circulation, but both measurements are influenced by the rigidity of the ocular coats. On the other hand, ChBF_p measures a fraction of the pulsatile choroidal blood flow in the subfoveal region. It is, however, likely to

reflect the true pulsatile choroidal component as it measures directly the velocity of the red blood cells within the choroidal vessels, and the extrapolation of ChBF_p does not depend on the movement of the corneoscleral shell.

OPA is the fluctuation of IOP within each cardiac cycle—the pulse-related IOP change.^{14,15} Studies have shown that OPA is proportionally related to IOP and inversely related to axial length.¹⁵ Even though POBF is calculated from OPA, OPA is not a direct indicator of pulsatile blood flow as ocular rigidity is a major confounding factor.⁸ OPA increases whereas POBF decreases with increased IOP.³ OPA is not associated with blood pressure, perfusion pressure, or pulse pressure.¹⁶

In this paper, we are presenting a novel noninvasive method of estimating ocular rigidity (E) using dynamic contour tonometry and LDF. Dynamic contour tonometry provides the measurement of OPA (ΔIOP). Subfoveal measurement of choroidal blood flow by LDF estimates the ΔV . ChBF_p is chosen as the ΔV instead of the difference between the systolic and the diastolic ChBF. The reason is that ChBF_p is a ratio and is less dependent on the signal strength than the absolute values of the systolic and diastolic ChBF. Substituting OPA and ChBF_p as ΔIOP and ΔV , respectively, into the Friedenwald's equation, an estimation of E that we name E_R was calculated in a cohort of patients with clinical diagnoses ranging from normal (N), glaucoma suspect (GS), ocular hypertension (OHT) to advanced open-angle glaucoma (OAG). We hypothesized that patients with ocular hypertension would have a higher rigidity value since this increased rigidity might make them resistant to IOP-related optic nerve damage compared with patients with OAG.

METHODS

Patients

Normal subjects and patients with a diagnosis of OAG, GS, and OHT were recruited for the study. The diagnosis of OAG was based on nonoccludable angles on gonioscopy, glaucomatous optic nerve appearance on fundus exam, and corresponding visual field defect. GS had increased cup-to-disc ratio (CDR) or asymmetry of optic nerve appearance between two eyes but had normal visual fields. GS could have IOP above normal limit (greater or equal to 24 mm Hg) and might have been treated with topical IOP-lowering agent. Based on our definition, the GS group included preperimetric glaucoma patients, normal subjects with physiological increased CDR, and OHT patients with physiological increased CDR. We expected the E_R values of the GS group to be between that of OHT and glaucoma patients. OHT patients had IOP greater or equal to 24 mm Hg on three separate visits, nonoccludable angles on gonioscopy, normal optic disc appearance, and normal visual fields. Assessment and classification of optic nerve appearance was done by one of the three fellowship-trained glaucoma specialists (MRL, GL, PJH) on clinical exam. All patients had automated static visual field test (Humphrey SITA-Standard 24-2 program; Carl Zeiss Meditec, Inc., Dublin, CA). Normal subjects were recruited from the normative database of a community-based glaucoma-screening program. All normal subjects had IOP less than 23 mm Hg, normal optic nerve appearance on fundus exam, and normal visual field test. Exclusion criteria included one of the following: age younger than 35 years old; diagnosis of any other form of glaucoma other than OAG; previous history of intraocular surgery (including cataract extraction) or refractive surgery; optic neuropathy other than glaucoma; visual field anomaly other than glaucomatous visual field damage; any form of retinopathy with the exception of mild background diabetic retinopathy; and any patients unable to provide adequate quality imaging. The present study adhered to the principles of the Declaration of Helsinki and was approved by the ethics committee of Maisonneuve-Rosemont

TABLE 1. Characteristics of the Four Diagnostic Groups: Normal (N), Glaucoma Suspect (GS), Open-Angle Glaucoma (OAG), and Ocular Hypertension (OHT)

	N, N = 56	GS, N = 48	OAG, N = 108	OHT, N = 45	P Value
Age, y*	62.1 ± 6.3	59.4 ± 8.6	67.7 ± 9.4	65.6 ± 10.8	<0.001
Male/female ratio	21/35	16/32	43/65	22/23	0.59
Topical medication†	0 ± 0	0.4 ± 0.5	1.3 ± 0.9	0.9 ± 0.7	<0.001
IOPMax, mm Hg†	15.3 ± 4	20.0 ± 7	23.5 ± 8	30.0 ± 6	<0.001
IOP_DCT, mm Hg†	16.9 ± 4.3	18.3 ± 4.6	17.4 ± 4.5	22.1 ± 4.5	<0.001
IOP_GAT, mm Hg†	14.0 ± 4.1	16.0 ± 3.4	15.0 ± 4.0	20.0 ± 4.0	<0.001
Axial length, mm†	23.5 ± 1.6	23.9 ± 1.7	23.8 ± 1.6	23.4 ± 1.3	0.07
CCT, μm*	549.3 ± 32.3	549.4 ± 31.1	533.6 ± 36.3	550.8 ± 42.9	0.006
MD, dB†	-	-0.51 ± 1.76	-4.26 ± 7.66	-0.35 ± 2.19	<0.001
OP, mm Hg†	2.9 ± 1.6	3.4 ± 1.6	2.9 ± 1.3	4.2 ± 2.1	<0.001
ChBF _p †	0.287 ± 0.153	0.323 ± 0.130	0.363 ± 0.180	0.294 ± 0.153	0.06
SBP, mm Hg†	128 ± 21	130 ± 30	135 ± 25	137 ± 27	0.03
DBP, mm Hg*	76.5 ± 8.4	77.3 ± 7.3	76.1 ± 8.5	77.4 ± 7.0	0.77
MAP, mm Hg†	94.3 ± 12.0	96.5 ± 15.2	95.2 ± 11.6	97.7 ± 11.2	0.22
MOPP, mm Hg*	45.3 ± 6.2	44.9 ± 7.4	45.9 ± 7.9	42.6 ± 6.6	0.08

IOPMax, highest recorded IOP; IOP_DCT, intraocular pressure measured using dynamic contour tonometry; IOP_GAT, intraocular pressure measured using Goldmann applanation tonometry.

* Data is expressed as mean ± SD. *P* value obtained via ANOVA.

† Data is expressed as median ± IQR. *P* value obtained via Kruskal-Wallis test.

Research Center. All subjects were informed of the purpose of the study and gave informed consent.

Data including age, ethnicity, family history of glaucoma, medical history, and topical medications were obtained from each subject. Mean deviation (MD) of the most recent and reliable visual field testing was recorded. In one session, each subject underwent IOP measurements using both Goldmann applanation tonometry (GAT) and PASCAL dynamic contour tonometry (DCT; Ziemer Ophthalmic Systems AG, Port, Switzerland), measurement of subfoveal choroidal blood flow using LDF (Oculix Inc., Sion, Switzerland); central corneal thickness (CCT) using standard ultrasonic pachymeter; and axial length (AL) using ultrasonic A-Scan biometry (OcuSan; Alcon Surgical Inc., Irvine, CA). All measurements were taken with each subject seated. Brachial systolic and diastolic blood pressures (SBP, DBP, respectively) were also recorded for each subject while seated using an automatic sphygmomanometer device (Welch Allyn Inc., Skaneateles Falls, NY). Mean arterial blood pressure (MAP) was calculated using the following formula: $MAP = 2/3 DBP + 1/3 SBP$. Mean ocular perfusion pressure (MOPP) was obtained by subtracting IOP from MAP: $MOPP = 2/3 (MAP) - IOP$. The factor 2/3 accounts for the drop of BP in the ocular circulation when subjects were seated.¹⁷

Ocular Pulse Amplitude

DCT is a slit-lamp-mounted, nonapplanation contact tonometer that can measure the IOP variation within each cardiac cycle.¹⁸ It displays simultaneously the mean diastolic IOP value and OPA. DCT also provides an indicator of measurement quality as Q factor. Only records with a good-quality index (Q1 or Q2) were taken into account in this study.

Pulsatile Choroidal Blood Flow by Laser Doppler Flowmetry

The principles of LDF and its application in human subjects have been described in detail elsewhere.¹¹ Briefly, a diode laser beam (wavelength = 811 nm, 60 μW at the cornea) is delivered to an undilated eye through a fundus camera (Model TRC; Topcon, Tokyo, Japan). By asking the subject to fixate at the incoming diode laser beam, the continuous laser light was projected onto the subject's foveolar region and measured the subfoveal choroidal blood flow. The diameter of the laser beam at the fundus is approximately 200 μm in an emmetropic eye.

Subjects were asked to fixate at the incoming laser beam. The position of the laser was imaged on a monitor screen that enables the technician to ascertain the proper fixation of each subject. A minimum 60-second measurement of choroidal circulation was obtained. Analysis of the data was done by one of the authors (JW) using LDF software (version 2.1; Oculix Inc.). For each subject, a minimum 10 to 15 seconds of measurement was selected for analysis, choosing sequences of measurements that were relatively free of noise. The average of ChBF_p was computed by the software (LDF software, version 2.1; Oculix Inc.) (Formula: $ChBF_p = [systolic ChBF - diastolic ChBF] / systolic ChBF$) and used in the calculation of E_R .

Data Analysis

E_R was calculated to estimate the coefficient of ocular rigidity (E) according to the Friedenwald equation using OPA and ChBF_p:

$$E_R = (\log IOP_1 - \log IOP_2) / ChBF_p, \quad (2)$$

where IOP_1 and IOP_2 corresponded to systolic and diastolic IOP, respectively. IOP_2 was displayed automatically by DCT and IOP_1 was calculated as: $IOP_1 = IOP_2 + OPA$. The right eye of each patient was arbitrarily selected for analysis; when the data for the right eye was missing, the data of left eye was used. The distribution of each variable was assessed prior to the statistical analysis. The ANOVA was used for variables that followed a normal distribution and the nonparametric test (Kruskal-Wallis) was used for variables that were not normally distributed. Post hoc analysis was carried out using either a *t*-test or Mann-Whitney *U* test, depending on the variable's distribution. The characteristics of the four diagnostic groups and the values of E_R between these groups were compared using the appropriate statistical tests mentioned. All parameters are given in numerical values as either median ± IQR or mean ± SD, depending on the statistical test used. E_R was the main outcome variable and its association with AL, MD, age, CCT, and MAP was assessed using nonparametric Spearman correlation analysis. Multiple linear regression analysis was then used to determine whether the four diagnostic groups had different E_R values while adjusting for potential confounders.

RESULTS

A total of 257 subjects were included in the study: 56 N, 108 OAG, 48 GS, and 45 OHT. The average age was 64.5 ± 9.5

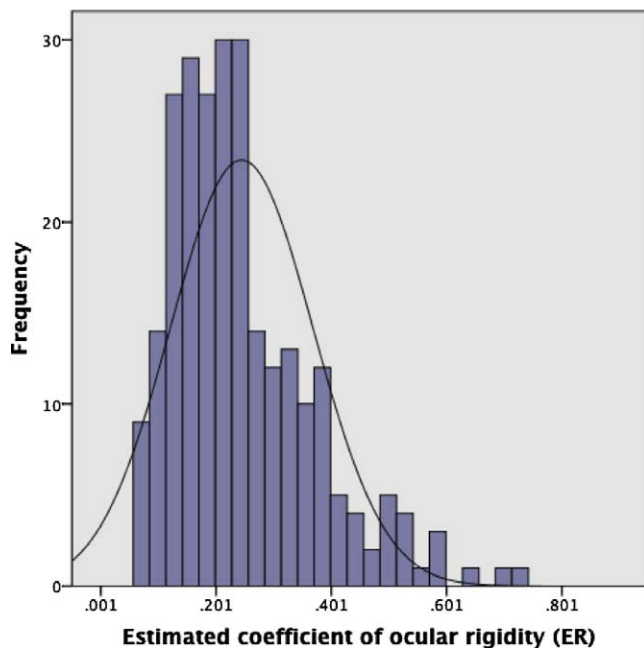


FIGURE 1. Histogram showing the distribution of E_R across the four diagnostic groups.

years. The majority of patients were Caucasians (240; 93.4%); a few were of African descent (15; 5.8%) or Asians (2; 0.8%). A portion of OAG eyes (46.3%; 50/108) never had historical IOP greater than 22 mm Hg and two patients classified as normal had IOP of 22 mm Hg. Baseline characteristics of each diagnostic group are presented in Table 1.

Sex, diastolic blood pressure, MAP, MOPP, and axial length were not significantly different between the four groups. Systolic blood pressure was higher in OHT group compared with normal subjects ($P = 0.03$). OAG subjects were significantly older than the three other groups and had worse visual field group mean, MD. In both DCT- and GAT-measured IOP, OHT subjects had the highest IOP. (This was due to the fact that OHT subjects were treated less aggressively in IOP lowering compared with OAG subjects). DCT-measured IOP was not significantly different between N, GS, and OAG, whereas GAT-measured IOP showed significantly lower IOP in N compared with GS and OAG (Table 1).

The distribution of E_R followed a skewed curve (Fig. 1). Its median value across the four diagnostic groups was 0.217 ± 0.15 . E_R was highest in patients with OHT (0.235 ± 0.16) and lowest in patients with OAG (0.188 ± 0.14), with the values of GS and N in between those two groups ($P = 0.01$; Table 2). We have also subdivided the OAG group into two subgroups: one group who never had historical IOP greater than 22 mm Hg and the second group who had higher historical IOP. We have found that the E_R in the OAG with low historical IOP group was even lower than the high historical IOP OAG group (0.176 ± 0.12 vs. 0.200 ± 0.15), but their difference did not reach a statistical significance ($P = 0.30$).

TABLE 2. The Median E_R Values according to the Four Clinical Diagnostic Groups: Normal (N), Glaucoma Suspect (GS), Open-Angle Glaucoma (OAG), and Ocular Hypertension (OHT)

	N, N = 56	GS, N = 48	OAG, N = 108	OHT, N = 45	P Value
E_R	0.230 ± 0.12	0.232 ± 0.15	0.188 ± 0.14	0.235 ± 0.16	0.01

Data is expressed as median \pm IQR. P value obtained via Kruskal-Wallis test.

TABLE 3. Multiple Regression Analysis with Logarithmic Transformed E_R as the Dependent Variable and with Diagnosis, Age, Blood Pressure, IOP, and CCT as Independent Variables

	Log Transformed E_R^* Standardized β Coefficient	P Value
Diagnostic group		
OAG	-	-
N	0.111	0.13
GS	0.197	0.007
OHT	0.288	<0.001
Age	-0.028	0.71
SBP	0.098	0.22
DBP	-0.176	0.02
IOP_DCT	-0.216	0.003
CCT	0.077	0.30

* The logarithmic of the original E_R data is used as the dependent variable in order to normalize the distribution of E_R .

Table 3 showed the results of multiple regression analysis using normalized E_R as the dependent variable and diagnostic group, age, SBP, DBP, IOP, and CCT as independent variables (Table 3). The regression analysis showed that the OHT group has a significantly greater E_R compared with the OAG group after controlling for the differences in age, IOP, BP, and CCT between the four groups.

E_R correlated negatively with AL in the entire cohort of patients ($\rho = -0.342$; $P < 0.001$), signifying that a longer eye had a lower estimated rigidity value (Fig. 2). E_R also correlated positively with MD in the entire study population ($\rho = 0.272$; $P < 0.001$), demonstrating an association between a more elastic (less rigid) eye and worse visual field MD. E_R did not correlate significantly with age ($P = 0.56$) or MAP ($P = 0.26$). A weak positive correlation was found between E_R and CCT ($\rho = 0.121$; $P = 0.05$) in our cohort of patients. A weak but significant negative correlation existed between E_R and DCT-measured IOP ($\rho = -0.161$; $P = 0.01$) but not between E_R and GAT-measured IOP ($\rho = -0.102$; $P = 0.27$).

DISCUSSION

We found that our new parameter, E_R , was highest in ocular hypertensive patients and lowest in glaucoma patients, and that patients with longer axial length had lower E_R values signifying that they were more elastic. The limitation of using laser Doppler flowmetry to determine E_R is that the signal for each parameter (ChBVel, ChBVol, and ChBF) is influenced by the tissue-scattering properties. The interindividual comparison of the absolute blood flow values may not be appropriate due to this reason. This potential bias was minimized in the current study by eliminating subjects with macular diseases and by using the pulsatile ChBF (ChBF_p) value, which is a ratio, instead of the systolic, diastolic, or mean ChBF. ChBF_p is measured at the subfoveal region and only reflects a small part of the pulsatile blood flow of the entire choroid, unlike FPA, which reflects the entire choroidal circulation. Our estimation

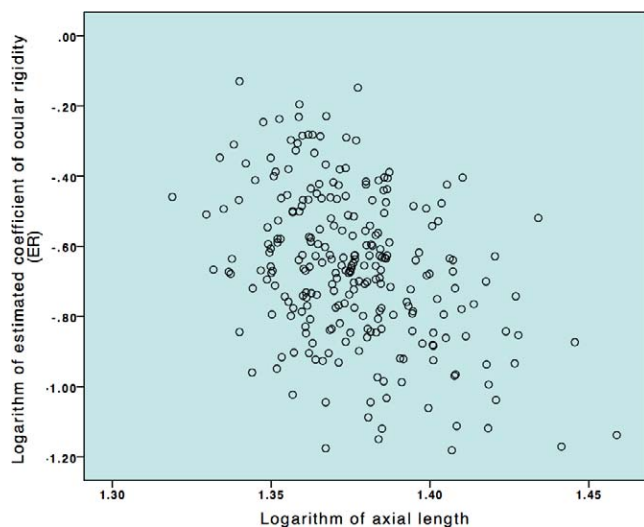


FIGURE 2. Correlation between E_R and AL (Spearman $\rho = -0.342$; $P < 0.001$). The negative correlation suggests that a longer eye has lower rigidity estimated using E_R . Values were normalized using logarithmic transformation of the original E_R and axial length data.

of ΔV using a small fraction of choroidal blood flow explains in part the disparities between the values of the estimate of E obtained in our study and those obtained by others.^{2-4,6,19} However, using ChBF_p has other advantages as discussed in the introduction.

Regarding the reproducibility of our method of estimating E , OPA, DCT-measured IOP, and ChBF_p measurements used in the calculation have been shown to be reproducible in healthy subjects and in patients with ocular diseases.^{20,21} The reproducibility of ChBF_p measurement by laser Doppler flowmetry and OPA have also been evaluated in our laboratory on a cohort of patients with open-angle glaucoma and normal control subjects: the ICC of ChBF_p was 0.80 (0.65–0.89) and that of OPA was 0.84 (0.73–0.92; Descovich D, et al. *IOVS* 2009;50:ARVO E-Abstract 5866).

Studies have shown that the biomechanical susceptibility of the optic nerve head to IOP may be a key factor in the pathogenesis of glaucomatous optic neuropathy.²² Histological studies on postmortem glaucomatous eyes have shown altered lamina cribrosa (LC) structure composition, compression, and thinning of LC compared with normal controls.^{23,24} Studies on the movement of LC in response to increased IOP have also been performed in enucleated human eyes.^{25,26} In addition to the finding that LC bowed posteriorly in response to IOP elevation, both studies have reported that movement of LC was mostly present in the clinically relevant range of IOPs and that a large interindividual variability in the movement of LC existed. Recently, modeling of the optic nerve head (ONH) using a finite element (FE) method has also provided insight into ONH susceptibility to IOP. Generic modeling of ONH parameterized geometrical factors and material properties were weighted for their relative impact on the deformation of ONH. Based on this model, scleral stiffness had by far the greatest impact on ONH biomechanics, ahead of LC stiffness, axial length, and IOP.¹ The model predicted that deformation (strain) of LC and prelaminar neural tissue decreased as the sclera stiffened and increased exponentially as the sclera became more elastic. The prediction of their model is compatible with the results of our current study where the ratio calculated according to Friedenwald's equation on ocular rigidity (E_R) is lowest in patients with glaucoma and highest in patients with ocular hypertension.

Studies on the relationship between ocular rigidity and OAG have presented contradictory results. Drance estimated scleral rigidity in vivo using Schiotz and applanation tonometries and found that ocular rigidity (E) was lower in untreated glaucoma patients compared with normal and was also lower in patients with myopia.¹⁹ Noninvasive methods of estimating rigidity in vivo by Hommer and Ebnetter have found that glaucoma patients had higher E compared with normal subjects.^{6,7} In the study in enucleated eyes, Zeimer et al. found that the displacement of the optic nerve head was smaller in the more advanced glaucoma cases and was the same as normal in early stage of glaucoma.²⁷ They interpreted their results as supporting the hypothesis that increased ONH rigidity was a consequence of longstanding glaucoma. However, due to the specifics of their experimental setup and the fact that they did not measure scleral elasticity but measured the displacement of ONH relative to the scleral displacement, other interpretations of their data are possible. Recent biomechanical studies have demonstrated a hypercompliant deformation of LC and scleral canal in monkeys with early experimental glaucoma that returned to normal after a couple of weeks.²⁸ In enucleated porcine eyes, stiffening of sclera by collagen cross-linking techniques led to decreased LC and peripapillary scleral movement.²⁹ This result further supported the hypothesis proposed by FE modeling of ONH that a more elastic sclera was associated with increased strain of ONH.

Increased AL is associated with myopia. Histological studies have found that peripapillary scleral thickness as well as LC thickness was decreased in eyes with longer AL.²⁴ Active scleral remodeling following axial elongation has been shown in animal eyes.³⁰ The results of these studies suggested that increased axial length was associated with a thinner sclera and possibly altered biomechanical properties, especially an increased viscoelasticity.³¹ The association between myopia and OAG could be partially explained by this change in scleral biomechanics that potentially makes the myopic ONH more prone to glaucomatous damage. In the present study, we found that increased axial length was, indeed, associated with decreased E_R measured by our technique.

Our study did not show a significant correlation between E_R and age, perhaps because our age range only included older adults. However, a number of studies have consistently shown that aging was associated with increased rigidity of the ocular coats estimated using manometric methods.^{4,32} Histological studies have also shown altered collagen composition in the LC in older human eyes.^{32,33} Based on the facts that scleral stiffness increases with age and that the prevalence of OAG increases with age, a common assumption is that increased scleral stiffness may be a risk factor for OAG. However, our data indicates that E_R is lowest in glaucoma patients. One can hypothesize that increased stiffness may be a protective factor for OAG and inadequate increase in stiffness with age may predispose the individual to the development of glaucomatous optic neuropathy. This hypothesis should be tested with further studies.

The coefficient of ocular rigidity was previously shown to increase with increased baseline IOP in enucleated eyes, anesthetized rabbit eyes and healthy human subjects undergoing cataract surgery.^{2,3,19,34} In these studies, a large range of IOP—ranging from 15 to 55 mm Hg—was artificially increased and a change in the shape of pressure-volume relationship (i.e., an increase in E) was observed as IOP increased. The weak but negative relationship between E_R and IOP observed in our study could be due to the fact that we have a much narrower range of IOP. Most of our patients had IOP ranging from 12 mm Hg to 24 mm Hg (mean \pm 2 SD) with less than 10 subjects who had IOP greater than 25 mm Hg. In two studies estimating E in

vivo, the correlation between IOP and E were not reported because of the study design.^{6,7}

In conclusion, E_R , the relationship of OPA and $ChBF_P$, calculated according to the Friedenwald's ocular rigidity equation, may be a useful estimate of ocular rigidity (E). We have found highest E_R in patients with ocular hypertension and lowest in patients with glaucoma. Our results are compatible with the results of finite element modeling of the ONH showing that decreased scleral rigidity was associated with increased strain on the ONH and LC and might be associated with an increased susceptibility of the ONH to IOP-related damage. We have also found lower E_R values in patients with longer axial length, signifying that longer myopic eyes were more elastic compared with shorter eyes. Future prospective studies should evaluate the role of ocular rigidity in the development and progression of glaucoma.

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