Evaluation of the Influence of Corneal Biomechanical Properties on Intraocular Pressure Measurements Using the Ocular Response Analyzer

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Purpose: The Ocular Response Analyzer (ORA) proposes to measure corneal biomechanical properties in vivo by monitoring and analyzing the corneal behavior when this structure is submitted to a force induced by an air jet. The purpose of this study was to evaluate the relationship between corneal biomechanical properties and corneal-compensated intraocular pressure (IOPCC) measurements as obtained by the ORA and Goldmann applanation tonometry (GAT) measurements.

Design: Observational clinical study.

Methods: The study included 153 eyes of 78 subjects. All subjects underwent IOP evaluation with the ORA and GAT, and also measurements of central corneal thickness (CCT), corneal curvature, and axial length. Univariable and multivariable regression analysis were used to evaluate the associations between IOP (as measured with GAT and ORA) and CCT, corneal curvature, axial length, and age. Bland and Altman plots were used to evaluate the agreement between IOP measurements obtained by GAT and ORA.

Results: GAT IOP measurements were significantly associated with CCT ($P = 0.001$) and corneal curvature ($P < 0.001$), whereas ORA IOPCC measurements were not associated with any of the ocular variables. The difference between GAT and IOPCC measurements was significantly influenced by corneal thickness. Patients with thicker corneas tended to have higher GAT IOP measurements compared with IOPCC, whereas in patients with thin corneas, GAT IOP measurements tended to be lower than IOPCC.

Conclusions: ORA IOPCC measurements seem to provide an estimate of IOP that is less influenced by corneal properties than those provided by GAT.

Key Words: intraocular pressure, tonometry, corneal thickness, corneal elasticity

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The influence of central corneal thickness (CCT) on intraocular pressure (IOP) measurements using Goldmann applanation tonometry (GAT) is well recognized.[1–3] Intraocular pressure may be overestimated or underestimated in thick or thin corneas, respectively. Whitacre et al[1] showed that the extremes of underestimation and overestimation span a range of almost 12 mm Hg, indicating that measuring CCT may well have important implications for assessing IOP.

The thickness of the cornea, however, is just one among several corneal physical properties that influence the measurement of IOP with applanation tonometry. Other biomechanical parameters such as elasticity or viscoelastic properties may also influence corneal resistance to applanation and, therefore, IOP measurements obtained by GAT.[2–4] In fact, a recent study suggests that the error in intraocular pressure measurement induced by variation in corneal elasticity can be as high as 17 mm Hg, even when corneal thickness and other parameters are kept constant.[2] Further, the influence of CCT on IOP measurement was demonstrated to be different according to the levels of corneal elasticity or "stiffness."

The recently developed Ocular Response Analyzer (ORA; Reichert Inc, Depew, NY) proposes to measure corneal biomechanical properties in vivo.[5] It is based on the principle that information on biomechanical properties can be extracted by monitoring and analyzing the corneal behavior when this structure is submitted to a force induced by an air jet. Previous investigations demonstrated changes in corneal biomechanical properties, as assessed by the ORA, in patients with keratoconus or Fuch's corneal dystrophy and after refractive procedures such as LASIK.[5] The ORA also produces a measure of intraocular pressure that is proposed to be independent of the corneal biomechanical properties.

The purpose of the present study was to evaluate the relationship between corneal biomechanical properties and IOP measurements as obtained by ORA and Goldmann IOP measurements. We also evaluated the relationship between these measures and other ocular parameters including corneal thickness, corneal curvature, and axial length.

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METHODS

This was an observational clinical study. All subjects were evaluated at the Hamilton Glaucoma Center, University of California, San Diego, from January 2004 to September 2005. The Human Subjects Committee of the University of California, San Diego approved all protocols and the methods described adhered to the tenets of the Declaration of Helsinki.

Each subject underwent a comprehensive ophthalmologic examination including review of medical history, best corrected visual acuity, slit-lamp biomicroscopy, gonioscopy, dilated fundoscopic examination using a 78D lens, stereoscopic optic disc photography, and automated perimetry using 24-2 Swedish Interactive Threshold Algorithm (SITA) (Carl Zeiss Meditec Inc, Dublin, CA). To be included, subjects had to have best corrected visual acuity of 20/40 or better, spherical refraction within $\pm$ 5.0 D and cylinder correction within $\pm$ 3.0 D, and open-angles on gonioscopy. Subjects were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery) or refractive surgery. Patients with secondary causes of high intraocular pressure (eg, iridocyclitis, trauma) or other intraocular eye disease were excluded.

As IOP was the main variable being studied, it was not used as inclusion criterion for the study. However, all subjects were required to have normal and reliable visual fields and normal appearance of the optic disc on stereophotographs (no diffuse or focal rim thinning, hemorrhage, cupping, or nerve fiber layer defects indicative of glaucoma or other ocular pathologies). Simultaneous stereoscopic optic disc photographs (TRC-SS; Topcon Instrument Corp of America, Paramus, NJ) were evaluated by two experienced graders, and each grader was masked to the subject's identity and to the other test results. All included photographs were judged to be of adequate quality or better. Discrepancies between the 2 graders were either resolved by consensus or by adjudication by a third experienced grader. Reliable visual fields were required to have fixation losses, false positives and false negatives below 25%. A normal visual field was defined as a mean deviation and pattern standard deviation within 95% confidence limits, and a Glaucoma Hemifield Test within normal limits.

All subjects had CCT, corneal curvature, and axial length measurements performed by a trained technician during the same visit, but before IOP measurements. CCT measurements were obtained using ultrasound pachymetry (Pachette GDH 500, DGH Technology, Inc, Philadelphia, PA). The pachymeter probe was placed on the center of the cornea over an undilated pupil and the mean of 3 readings was calculated for each eye. Corneal curvature measurements were obtained using an autorefractor (Humphrey-Zeiss model S97, Carl-Zeiss Meditec, Dublin, CA). Axial length measurements were acquired with IOLMaster (Carl-Zeiss Meditec, Dublin, CA).

Subjects underwent testing with the ORA by a trained technician. Two measurements were obtained for each eye and the average of the 2 measurements per eye was considered for analysis. Subsequently, intraocular pressure measurements were obtained with Goldmann applanation tonometer (GAT; Haag-Streit, Konig, Switzerland) by one of the investigators. The investigator obtaining GAT IOP measurements was masked to the results of the ORA examination and to the results of other tests. Two measurements were obtained for each eye and the average of the 2 measurements per eye was considered for analysis. If the 2 measurements differed by more than 3 mm Hg, a third measurement was taken and the average of the 2 closest measurements was considered as the final value for analysis.

ORA

The ORA determines corneal biomechanical properties using an applied force-displacement relationship. Details of its operation have been previously described.[5] During an ORA measurement, a precisely metered air pulse is delivered to the eye, causing the cornea to move inward, past a first applanation and move into a slight concavity. Milliseconds after the first applanation, the air pump generating the air pulse is shut down and the pressure applied to the eye decreases in an inverse-time, symmetrical fashion. As the pressure decreases, the cornea passes through a second applanated state while returning from concavity to its normal convex curvature. The 2 applanations take place within approximately 20 milliseconds, a time sufficiently short to ensure that ocular pulse effects or eye position does not change during the measurement process. An electro-optical collimation detector system monitors the corneal curvature in the central 3.0 mm diameter throughout the 20 milliseconds measurement period, based on the reflection of light from the cornea. When the cornea is flat (applanated), the reflection of light is maximal, generating a peak. A filtered version of the detector signal defines 2 precise applanation times corresponding to 2 well-defined peaks produced by inward and outward applanation events. Two corresponding pressures of an internal air supply plenum are determined from the applanation times derived from the detector applanation peaks. These 2 pressures are defined as the intersection of a vertical line drawn through the peaks of the applanation curve with the plenum pressure curve. The 2 applanation pressures are different primarily because of the biomechanical properties of the cornea. A measurement called corneal-compensated intraocular pressure (IOPCC) is obtained from the difference between the 2 applanation pressures using the formula $P2 - kP1$, where $P1$ and $P2$ are the first and second applanation pressures, respectively, and k is a constant. As the difference between $P1$ and $P2$ is related to the corneal biomechanical properties, the value of IOPCC is supposed to represent a measure of intraocular pressure that is free of the corneal influence. The constant k has a value of 0.43, which was derived from a study on intraocular pressure changes before and after refractive (LASIK) surgery (D. Luce, PhD, Reichert Inc, written communication, September 2005). The ORA also provides a measure called corneal resistance factor (CRF)

TABLE 1. Clinical Characteristics of the 153 Eyes Included in the Study

Parameter	Mean ± Standard Deviation	Range
CCT (μm)	538 ± 35	414-627
Corneal curvature (mm)	7.74 ± 0.33	7.00-9.04
Axial length (mm)	23.82 ± 1.08	20.92-26.70
GAT IOP (mm Hg)	15.3 ± 3.3	8.0-26.0
ORA IOPCC (mm Hg)	15.2 ± 3.0	7.4-29.3
CRF (mm Hg)	9.47 ± 1.75	4.68-14.15

that is derived from the difference between P1and P2 and is supposed to represent a measure of corneal biomechanical properties.

Statistical Analysis

Regression analysis was used to evaluate the associations between IOP (as measured with GAT and ORA) and CCT, corneal curvature, axial length, and age. Initially, the associations were investigated using univariable analysis. Subsequently, all independent variables were entered in multiple regression models to assess their relationship with IOP, as measured by the different devices. No variable selection method was used. As the models were developed for hypothesis testing, there was little concern for parsimony. The full-prespecified model fit, including all variables, results in more accurate *P* values for tests of variables of interest.[6]

To adjust for the fact that both eyes of the same individual were included in the analyses, we used generalized estimating equations with an exchangeable working correlation structure to describe the correlation of measurements between both eyes.[7,8]

Bland and Altman[9] plots were used to evaluate the agreement between IOP measurements obtained by GAT and ORA. The differences between measurements for each parameter were plotted against their mean. These plots enable any systematic difference between the measurements (ie, a fixed bias) to be ascertained. The mean difference is the estimated bias and the standard deviation (SD) of the differences measures the random fluctuations around this mean. If the mean value of the difference differs significantly from 0 on the basis of a one-sample *t* test, this indicates the presence of fixed bias. We also calculated 95% limits of agreement for each comparison (mean difference ± 1.96 SD), which indicate how far apart measurements by 2 methods were more likely to be for most individuals. Bland and Altman plots were also used to investigate any possible relationship of the discrepancies between the measurements and the mean value (ie, a proportional bias). The existence of proportional bias indicates that the methods do not agree equally through the range of measurements, that is, the limits of agreement will depend on the actual measurement. To formally evaluate this relationship, the difference between the methods was regressed on the average of the 2 methods.

Statistical Analyses were performed using STATA v. 9.0 (StataCorp, College Station, TX) and SPSS v.13.0 (SPSS Inc, Chicago, IL). A *P* value less than 0.05 was considered statistically significant.

RESULTS

The study included 153 eyes of 78 subjects. Thirty-five patients were male (45%). There were 31 (40%) whites, 44 (56%) African Americans, 2 (3%) Asians, and 1 Hispanic (1%) subjects. The mean ± SD age of the included subjects was 54 ± 15 years, ranging from 20 to 81 years. Table 1 shows clinical characteristics of the included eyes.

Table 2 shows results of univariable regression for the associations between different IOP measurements and CCT, axial length, corneal curvature and age. Intraocular pressure measurements obtained by GAT were significantly correlated with CCT and corneal curvature. Each 100 μm increase in CCT resulted in 2.739 mm Hg increase in GAT IOP ($P = 0.001$). Figure 1A shows a scatterplot of GAT IOP measurements versus CCT. Each 1.0-mm increase in the radius of corneal curvature resulted in 3.336 mm Hg decrease in GAT IOP ($P < 0.001$). Axial length and age were not significantly associated with GAT IOP measurements. On the other hand, ORA IOPCC measurements were not significantly associated with CCT ($P = 0.106$), corneal curvature ($P = 0.112$), or axial length ($P = 0.117$). IOPCC measurements were, however, significantly associated with age ($P = 0.044$). Figure 1B shows a scatterplot of IOPCC values and CCT. Table 3 shows the results of multiple regression models. In multivariable analysis, GAT IOP measurements were significantly associated only with CCT ($P = 0.007$), whereas IOPCC measurements were not associated with any of the independent variables.

TABLE 2. Results of Univariable Regression Analysis of the Association Between Intraocular Pressure Measurements and Other Clinical/Ocular Variables*

	GAT IOP		ORA IOPCC	
	Coefficient (SE)	*P*	Coefficient (SE)	*P*
Age (per y)	0.039 (0.024)	0.105	0.046 (0.023)	0.044
CCT (per 100 μm)	2.739 (0.842)	0.001	1.144 (0.708)	0.106
Corneal curvature (per mm)	− 3.336 (0.746)	< 0.001	− 1.594 (1.004)	0.112
Axial length (per mm)	− 0.522 (0.303)	0.085	− 0.377 (0.241)	0.117

*Intraocular pressure measurements were entered as dependent variables and age, CCT, corneal curvature, and axial length as independent variables (one at a time, in univariable regression).

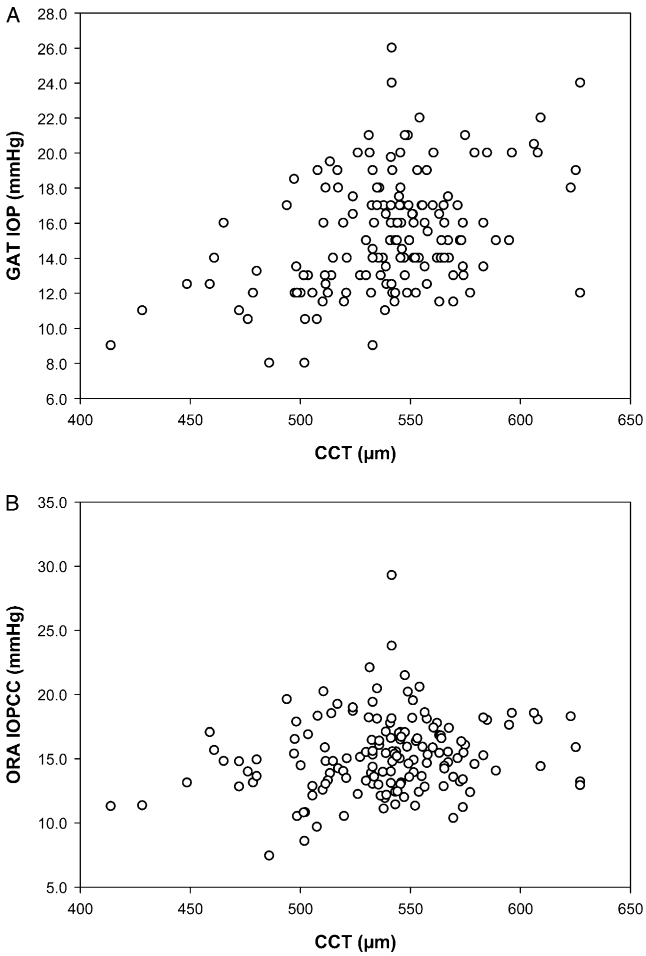

FIGURE 1. A, Scatterplot of GAT IOP versus CCT. B, Scatterplot of ORA IOPCC measurements and CCT.

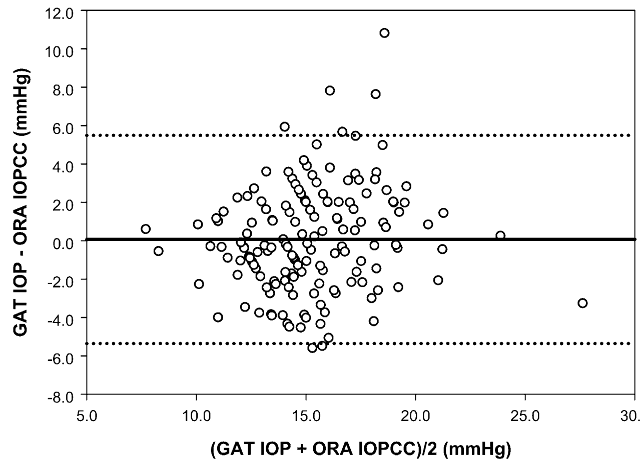

FIGURE 2. Bland-Altman plot of the agreement between GAT IOP measurements and ORA IOPCC measurements. The difference between the measurements is plotted against the average of the measurements. Dotted lines represent 95% limits of agreement.

Figure 2 shows a Bland-Altman plot of the agreement between GAT IOP and IOPCC. The mean ± SD difference between GAT IOP and IOPCC was 0.068 ± 2.77 mm Hg (95% limits of agreement: − 5.36 to 5.49 mm Hg). The mean difference was not significantly different from zero (P = 0.758). There was no evidence of proportional bias as indicated by the lack of correlation between the difference and the average of the measurements (P = 0.756). That is, the magnitude of IOP did not influence the difference between GAT and IOPCC measurements. The difference between GAT and IOPCC measurements was, however, significantly influenced by corneal thickness. Figure 3 shows a scatterplot of the difference GAT IOP-IOPCC versus CCT. Each 100-μm increase in corneal thickness resulted in 2.256 mm Hg increase in the difference GAT IOP-IOPCC (P = 0.005). Patients with thicker corneas tended to have higher GAT IOP measurements compared with IOPCC, whereas in patients with thin corneas, GAT IOP measurements tended to be lower than IOPCC.

Next, we evaluated the relationship between the ORA measure of corneal biomechanical properties, the CRF, and the other variables evaluated in the study. In univariable analysis, values of CRF were significantly associated with corneal thickness (r = 0.443; P < 0.001) and corneal curvature (r = − 0.392; P < 0.001), but not with axial length (r = − 0.226; P = 0.056) or age (r = 0.201; P = 0.112). Figure 4 shows a scatterplot of CRF and CCT values. GAT IOP measurements were significantly associated with CRF (P < 0.001). In a multiple regression model including GAT IOP as dependent variable and CRF, CCT, corneal curvature, axial length, and age as independent variables,

TABLE 3. Results of Multivariable Regression Analysis of the Association Between Intraocular Pressure Measurements and Clinical/Ocular Variables*

	GAT IOP		ORA IOPCC	
	Coefficient (SE)	***P***	**Coefficient (SE)**	***P***
Age (per y)	0.029 (0.024)	0.222	0.044 (0.024)	0.064
CCT (per 100 μm)	2.183 (0.803)	0.007	0.578 (0.668)	0.387
Corneal curvature (per mm)	− 1.982 (1.210)	0.101	− 0.240 (1.250)	0.848
Axial length (per mm)	− 0.236 (0.345)	0.496	− 0.319 (0.318)	0.316

*Intraocular pressure measurements were entered as dependent variables and age, CCT, corneal curvature, and axial length as independent variables. All independent variables were entered in the regression model.

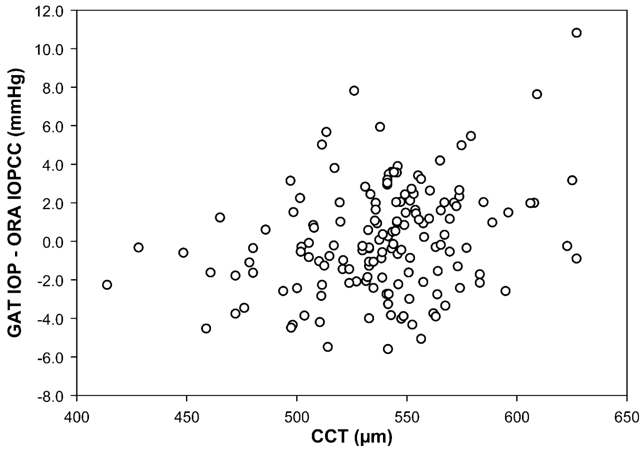

FIGURE 3. Scatterplot of the difference between GAT IOP measurements and ORA IOPCC measurements versus CCT.

only CRF was significantly associated with GAT measurements ($P < 0.001$) (Table 4). When the same multiple regression model was repeated, but using IOPCC instead of GAT IOP as dependent variable, none of the independent variables were significantly associated with IOPCC (Table 4).

DISCUSSION

In the present study, we demonstrated that the assessment of corneal biomechanical properties with the ORA was useful to evaluate the influence of corneal properties on IOP measurements. In addition, a IOPCC measurement provided by the ORA was demonstrated to be less influenced by corneal properties than IOP estimates obtained by the Goldmann tonometer. These findings may have significant implications on the use of these instruments in clinical practice.

Applanation tonometry measures IOP by subjecting the eye to a force that flattens the cornea. It assumes that the Imbert-Fick law is applicable to the eye.[3] This law states that the pressure within a sphere is approximately equal to the external force needed to flatten a portion of the sphere divided by the area of the sphere that is flattened. It is applicable to surfaces that are perfectly spherical, elastic, and infinitely thin. However, the cornea has a finite thickness and the eye is not a perfectly elastic structure. Several experimental studies from simultaneous manometry and applanation tonometry have shown that the applanating pressure is not always equal to the true intraocular pressure.[1,10,11] Ehlers et al[10] performed manometry and applanation tonometry on 29 eyes about to undergo cataract or glaucoma surgery and calculated that the Goldmann tonometer would only give accurate measurements when CCT was 520 μm. In a recent meta-analysis, Doughty and Zaman[12] found that each 10% difference of corneal thickness would result in approximately 1.1 mm Hg difference in IOP in normal subjects. That is, a change of approximately 100 μm in CCT would result in approximately 2.2 mm Hg change in IOP.

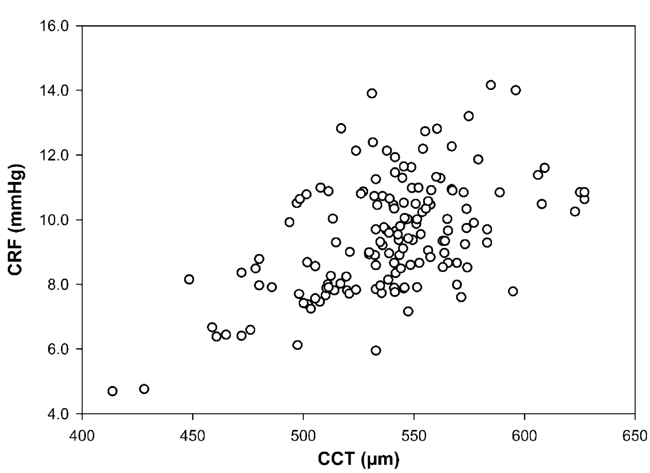

FIGURE 4. Scatterplot of CRF values versus CCT measurements.

In the present study, GAT IOP measurements were significantly influenced by CCT and the relationship between these 2 variables was similar to the one predicted by Doughty and Zaman and by other studies.[1,12,13] On the other hand, ORA IOPCC measurements were not significantly correlated with CCT both in univariable and in multivariable analysis, indicating that the IOPCC values provided by this instrument do not seem to be influenced by corneal thickness. Also, differences between GAT IOP and ORA IOPCC were significantly related to CCT. In patients with thin corneas, IOPCC values tended to be higher than GAT IOP, whereas for patients with thick corneas, IOPCC measurements tended to be lower than GAT IOP values.

Although research on the influence of corneal properties on GAT has been mainly focused on corneal thickness, there is evidence to suggest that other corneal properties may also affect IOP estimation with GAT, with an effect that can be even higher than the one induced by CCT variation.[2] A recent study by Liu and Roberts[2] attempted quantitatively to analyze the influence of corneal biomechanical properties on GAT IOP measurements through a mathematical model. The authors analyzed the separate influence of each one of the corneal parameters—thickness, radius of curvature, and modulus of elasticity—on IOP measurements obtained by applanation tonometry. They demonstrated that variations of the elasticity of the cornea within a range predicted to occur in a normal population would result in an error of IOP measurement as high as 17 mm Hg. This effect was even higher than the one induced by only variations in corneal thickness. Also, they demonstrated that the influence of CCT on applanation tonometry readings would depend on the modulus of elasticity of the cornea. For stiff corneas, the relationship between CCT and measured IOP would be much steeper than for soft ones. In the present study, GAT IOP measurements were significantly influenced by the ORA measure of overall corneal resistance, the CRF. In the multiple regression model incorporating CRF, CCT, and the other ocular variables, only CRF was significantly associated with

TABLE 4. Results of Multivariable Regression Analysis of the Association Between Intraocular Pressure Measurements and Clinical/Ocular Variables, Including Corneal Resistance Factor (CRF)*

	GAT IOP		ORA IOPCC	
	Coefficient (SE)	*P*	Coefficient (SE)	*P*
Age (per y)	0.021 (0.021)	0.317	0.043 (0.023)	0.062
CCT (per 100 μm)	0.903 (0.903)	0.317	0.352 (0.867)	0.685
Corneal curvature (per mm)	– 1.299 (1.192)	0.276	– 0.076 (1.338)	0.954
Axial length (per mm)	– 0.068 (0.291)	0.815	– 0.292 (0.305)	0.339
CRF (per mm Hg)	0.694 (0.189)	< 0.001	0.121 (0.235)	0.609

*Intraocular pressure measurements were entered as dependent variables and age, CCT, corneal curvature, axial length, and CRF as independent variables. All independent variables were entered in the regression model.

GAT IOP values. Also, a positive correlation was observed between CRF and CCT and between CRF and corneal curvature. These findings seem to indicate that CRF is not solely a measure of corneal material properties, but rather is an index that aggregates the effects of CCT, tissue material properties, and corneal curvature. On the other hand, ORA IOPCC values were not influenced by CRF, suggesting that ORA IOPCC measurements are not influenced by corneal properties.

Corneal curvature is another variable that can affect the accuracy of IOP measurements obtained by GAT.[3] In theory, the steeper the corneal curvature the more the cornea must be indented to produce the standard area of applanation. Therefore, more force must be applied against a steep than a flat cornea, increasing the indicated value of IOP. Also, when producing the standard area of applanation, more fluid is displaced from under a steep than a flat cornea, increasing the contribution of ocular rigidity in overestimating IOP. In the current study, we found that GAT IOP measurements were significantly influenced by corneal curvature values. Each 1-mm increase in the radius of corneal curvature (ie, a flatter cornea) resulted in 3.33 mm Hg decrease in IOP. This is in agreement with previous studies that also found a positive correlation between GAT IOP measurements and corneal curvature.[14] It should be noted, however, that the effect of corneal curvature on GAT IOP measurements was lower when adjusted for the effects of other variables in the multivariable model. This was most likely due to a significant positive correlation between corneal curvature and axial length ($r = 0.587$). On the other hand, ORA IOPCC measurements were not associated with corneal curvature both in univariable and in multivariable models, which seems to indicate that the effect of corneal curvature is also taken into account when corneal resistance properties are estimated by the ORA and incorporated in the IOP correction algorithm of this device.

GAT IOP measurement errors induced by corneal properties can lead to substantial misclassification of patients with great impact in the management of certain IOP-related conditions. Copt et al[15] showed that correcting IOP for corneal thickness, 31% of the patients with normal tension glaucoma would be reclassified as having primary open-angle glaucoma and 56% of ocular hypertensive patients would be reclassified as normal. Other studies demonstrated the major role of corneal thickness in the assessment of risk in patients with ocular hypertension,[16–19] which would be most likely related to the corneal-induced IOP measurement error in these patients. Because of the importance of corneal biomechanical properties, in addition to corneal thickness, it is likely that misclassification errors would be found to be even greater if biomechanical properties are also taken into account when correcting GAT IOP measurements. The lack of association between ORA IOPCC measurements and corneal properties suggest that misclassifications would be less common if this instrument is used to assess IOP. It should be emphasized, however, that prospective longitudinal studies are still necessary to validate the predictive value of IOP assessment with ORA in conditions such as ocular hypertension.

Our study has limitations. There was no independent reference method to assess true IOP to allow us to conclude which method of IOP evaluation was more representative of the true IOP status. Experimental studies involving concomitant manometric and tonometric readings will be necessary to evaluate this issue. However, manometric studies involving the current version of the ORA system are not feasible at this time as the system is not portable and measurements can only be obtained with the patient in sitting position. Also, the requirement of normal optic disc and visual field examinations as inclusion criteria excluded patients with glaucoma from our study. This was necessary to avoid introducing another confounding factor in the assessment of the relationship between corneal properties and tonometric-measured IOP. Future studies should attempt to validate ORA IOP measurements in these patients.

In conclusion, ORA evaluation of the corneal behavior when submitted to the stress produced by an air-jet pulse seems to provide a useful indication of corneal biomechanical properties. ORA IOPCC measurements seem to provide an estimate of IOP that is less influenced by corneal properties than those provided by GAT.

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