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ERRATUM

Correlations Between Corneal Biomechanical Properties Measured With the Ocular Response Analyzer and ICare Rebound Tonometry: Erratum

In the article that appeared on page 442 of the volume 17 number 6 issue of the *Journal of Glaucoma*, approval for research projects was obtained from an internal review board instead of the Ethics Committee of the University of Minhø as set forth in the Methods section.

Additionally, the following authors and degrees should have been listed as:

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REFERENCE

Jorge JMM, González-Méijome JM, Queirós A, et al. Correlations between corneal biomechanical properties measured with the ocular response analyzer and ICare rebound tonometry. *J Glaucoma*. 2008;17:442–448.

Correlations Between Corneal Biomechanical Properties Measured With the Ocular Response Analyzer and ICare Rebound Tonometry

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Purpose: To investigate the biomechanical properties of the normal cornea, and correlate them with central and peripheral corneal thickness and age.

Methods: Seventy-six right eyes of volunteers were measured with Ocular Response Analyzer (ORA), ICare rebound tonometry and an ultrasound pachymeter at corneal center and at 4 mm from corneal center in the nasal and temporal directions.

Results: ICare readings were significantly correlated with central and peripheral corneal thickness and corneal biomechanical properties. Corneal resistance factor was the biomechanical parameter with the higher correlation with ICare intraocular pressure (IOP) values. ICare tonometry at center and Goldmann equivalent IOP obtained with ORA were significantly higher for thicker than thinner corneas ($P < 0.05$). IOP compensated for corneal properties with the ORA was lower than the remaining IOP values measured in the study. Higher correlation was found between Goldmann equivalent IOP with ORA and ICare IOP values.

Conclusions: IOP values obtained with the rebound tonometer are higher in thicker corneas and are positively correlated with biomechanical corneal parameters, namely corneal resistance factor. Although corneal thickness plays a significant role in rebound tonometry, elastic and viscous properties of the cornea seem to play a significant role in the interaction of the tonometer probe with the ocular surface. However, the mechanism behind this process is presently unknown.

Key Words: corneal biomechanics, Ocular Response Analyzer, corneal thickness, rebound tonometry, intraocular pressure

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Disclosure: None of the authors has a commercial or financial interest in the instruments or materials used in the study.

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Intraocular pressure (IOP) measurements with conventional devices have demonstrated to be sensitive to corneal thickness variations.^{1–3} In fact, patients with reduced corneal thickness are at a higher risk of suffering from normal or low tension glaucoma and glaucoma damage.^{4,5} This is of major relevance in eyes that have undergone refractive surgery.⁶ However, the biomechanical properties of the cornea can also vary significantly without changes in corneal thickness and this could also affect IOP reliability. In fact, all tonometers that measure through the application of a stress to the corneal tissue are subject to the effects of corneal resistance. This corneal resistance is actually an “effective property” type of parameter. That is, rather than being a specific, intrinsic mechanical parameter like Young’s modulus, corneal resistance is a composite parameter that incorporates the material and geometric properties of the tissue, including the time and spatial dependence of the underlying corneal material properties.⁷

Different instruments have been recently developed for the direct measure of the biomechanical properties of the cornea. A review of those techniques can be found in the literature.⁸ However, most recent approaches are based on the noninvasive (air-puff) or invasive (direct contact of a tip) application of a controlled mechanical stress.^{8,9} The Reichert ORA (Reichert Inc, Depew, NY) determines corneal biomechanical properties using an applied force-displacement relationship by an air-puff similar to that used in traditional noncontact tonometry.⁹ Parameters used to characterize the biomechanical properties of the cornea include corneal hysteresis (CH) and corneal resistance factor (CRF). CH depends on the energy absorbed by the cornea when its tissue is submitted to stress and relaxation, thus inducing a delay in the corneal response to those forces.⁹ However, it is necessary to consider that CH and CRF are composite measures, which characterize the structural response of the eye to the measurement device rather than intrinsic material properties of the cornea, such as Young’s modulus. This means that what we call “biomechanical properties” do not represent a specific property of the corneal tissue, but the response of the entire corneal structure to the ORA’s measuring principle. As a result, these properties are only measurable by the ORA—a different device could potentially provide some other

measure of biomechanical properties. In addition, ORA provides 2 measurements of IOP, one that is equivalent to Goldmann applanation tonometry (GAT) (IOPg) and the other compensated for the corneal biomechanical properties of the cornea (IOPc).

Considering the new methods used for IOP measurement as rebound tonometry, new concerns arise because of the biomechanical properties of the cornea and the potential influence of such properties on rebound tonometry. ORA uses the delay of corneal response after the applanation process to estimate the amount of energy absorbed, and derive viscous and elastic properties of the cornea. In rebound tonometry, the absorbed energy could also delay the corneal response when the impact is applied to the cornea to measure IOP. According to this assumption, we could hypothesize that rebound of a small tip, as that used by the ICare tonometer (Tiolat Oy, Helsinki, Finland), could be affected by the biomechanical properties of the cornea. Despite this, no significant changes in IOP were found at thicker corneal periphery in normal corneas in the previous experiments carried out at our group.^{10,11} A complete description of this instrument and its functioning can be found in the literature.^{12–18}

In the present study, the Reichert's ORA was used to evaluate the correlations between corneal biomechanical properties with the IOP obtained with a rebound tonometer.

MATERIALS AND METHODS

Seventy-six right eyes of volunteers were evaluated with ORA and ICare rebound tonometer. ORA measurements were taken centrally as recommended by the manufacturer. Mean age was 33.0 ± 11.8 within a range from 19 to 60 years of age.

Inclusion criteria required that the subjects presented no corneal pathology or corneal scarring had no previous ocular surgery nor were taking any ocular medications. Despite some patients presented with high IOP values, none of them were taking any medication as this was the first time they had been made aware of this situation. After the purpose and procedures of the study were fully explained, each patient gave the consent to participate in the study. Study protocol followed the tenets of the Declaration of Helsinki and was reviewed by the Ethics Committee of the University of Minho.

ICare rebound tonometry was measured centrally (IC_c) and at 2 peripheral locations along the horizontal meridian in the nasal (IC_n) and temporal regions (IC_t). Peripheral measurements were taken at approximately 2 mm from limbus. In addition, ultrasound corneal thickness measurements at approximately the same locations (CT_c, CT_n, and CT_t) were obtained with a Tomey SP-100 Handy (Tomey, Nagoya, Japan), whose accuracy and repeatability had been recently assessed.¹⁹ Pachometry examinations were carried out after the application of topical tetracaine hydrochloride (0.5%). After sterilization using hydrogen peroxide (3%) and rinsing with saline, an ultrasound probe was applied as

perpendicular as possible to the cornea. Triplicate measurements were taken consecutively. To ensure precision in repositioning ultrasound probe at peripheral locations, all measurements were taken by the same investigator with the aid of a fixation panel. The patient was seated with the head placed on a chinrest 0.8 m away from the fixation panel. While their probe remains in the same position as it was when measuring central thickness, the eye turns to fixate each of the corresponding light-emitting diode's on the panel so that the probe can be placed at discrete locations over the cornea. Simple equations define the trigonometric relationship between the position of the fixation light-emitting diode's on the panel and the corneal location to be measured. This method has been probed to offer good reproducibility in peripheral computed tomography (CT) measurements.^{20–23} Tonometry measurements with ORA and ICare in a randomized order were always taken before ultrasound pachometry. All instruments were calibrated before commencement of the study.

Data were analyzed using the statistical package SPSS version 14.0 (SPSS Inc, Chicago, IL). Normality of data was evaluated with Kolmogorov-Smirnov test. Differences between IOP values with ORA and ICare were evaluated using 1-way analysis of variance (ANOVA) with Bonferroni post hoc correction. Parametric correlations were used for normally distributed variables, whereas nonparametric (Kruskall-Wallis) tests were used when normal distribution could not be assumed. Correlation coefficients were used to quantify the correlations among biomechanical, tonometric, and pachometric measurements, respectively. The sample was divided into 2 groups according to median central corneal thickness value. Values of IOP and biomechanical properties were compared for thinner and thicker corneas using 1-way ANOVA. The level of significance was established at $\alpha = 0.05$.

RESULTS

Descriptive statistics for the parameters measured in the study are presented in Table 1. Corneal thickness measurements were significantly different between the 3 corneal positions measured with peripheral nasal and temporal readings being thicker than central ones (ANOVA; $P < 0.001$); furthermore, nasal thickness was also significantly higher than temporal thickness taken at the same distance from limbus (ANOVA; $P < 0.001$). The 3 ICare readings were also significantly different between the center and the periphery (Kruskall-Wallis, $P = 0.018$) with temporal IOP being significantly higher than nasal and central readings. In addition, IOP readings were highly correlated among each other (Pearson coefficient > 0.800 ; $P < 0.001$).

Patient's age was positively correlated with IOPg (0.406, $P < 0.001$), IOPc (0.392, $P < 0.001$), corneal resistance factor (CRF) (0.277, $P < 0.015$), and IC_c (0.246, $P < 0.033$), but not with corneal thickness in any of the 3 locations measured ($P > 0.1$).

TABLE 1. Descriptive Statistics for the Parameters Measured With ORA, ICare, and US Pachometry

Instrument	Measure	ID	Mean	Standard Deviation	Minimum	Maximum
ORA (mm Hg)	IOP	IOP _g	15.47	3.43	8.40	23.20
		IOP _c	15.61	3.06	9.00	22.90
BP	CRF	CRF	10.68	1.97	5.50	16.60
	CH	CH	10.73	1.69	6.90	15.50
ICare rebound tonometer (mm Hg)	Center	IC _c	17.17	4.04	8.00	27.00
	Nasal	IC _n	16.83	3.89	10.00	29.00
	Temporal	IC _t	18.57	4.28	8.00	30.00
Ultrasound pachometer (μm)	Center	CT _c	535.69	35.08	448.33	610.67
	Nasal	CT _n	609.24	38.69	537.00	698.33
	Temporal	CT _t	574.80	38.43	484.00	662.33

Circles represent outliers.
 n = 76.
 BP indicates biomechanical properties.

Figure 1 displays a graphical representation of the IOP values obtained with the ORA and ICare. Temporal IOP obtained with ICare was significantly higher than IOP_g and IOP_c obtained with ORA (ANOVA, $P = 0.001$ and $P < 0.001$, respectively). Marginally significant differences were also detected between ICare IOP readings obtained in the nasal and temporal locations (ANOVA, $P = 0.028$). From this graphic representation, we can conclude that ICare displays higher and more variable results than ORA. IOP_g and IOP_c seem to be more reliable with the lower interquartile ranges and the least differences between maximum and minimum values and no outliers.

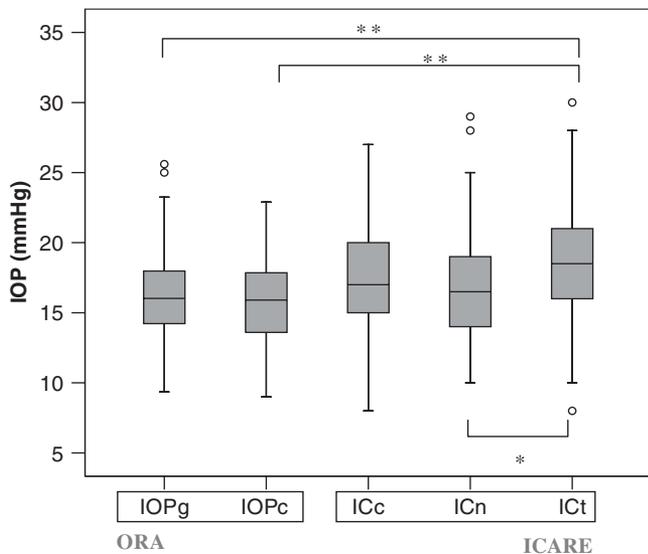


FIGURE 1. Boxplots of IOP values and statistical comparison among each other. ANOVA, post hoc Bonferroni corrected P values. *Mean values are statistically significant (ANOVA, $P < 0.05$). **Mean values are statistically significant (ANOVA, $P < 0.001$).

Regarding the agreement between IOP values obtained with ORA and ICare, stronger correlations were found between IOP_g than IOP_c, although all correlations were high and statistically significant ($P < 0.001$). Regression analysis presented in Figure 2 depicts the same results.

Table 2 displays the significant correlations among the biomechanical parameters (CRF and CH) and the remaining parameters under investigation. Stronger correlations were found for CRF than for CH with the IOP values obtained with the ICare rebound tonometer. These relationships are illustrated in Figure 3.

Correlations of the ICare IOP readings with corneal thickness are presented in Table 3 with both parameters being significantly correlated, particularly with corneal thickness at center and nasal locations. Figure 4 shows the relationship between ICare readings and corneal thickness. Despite the significance of correlation and regression analyses, this relationship is weaker than that observed with CRF presented in Table 2 and Figure 3.

Median value for central corneal thickness was 540 μm. The sample was divided into 2 groups and the different values of IOP were averaged to evaluate if any difference was present among thinner (≤ 540 μm) and thicker corneas (> 540 μm). Values as presented in Figure 5. According to this division, IOP_g, CRF, CH, IC_c, IC_n, and IC_t were significantly higher for thicker than thinner corneas (ANOVA, $P < 0.05$). An additional statistical analysis was repeated by splitting the eyes into groups considering grouping the eyes into 4 groups of equal number by corneal thickness and assigning the lower quartile to the thin cornea group, and the highest quartile to the thick cornea group not to bias the results by inclusion of the central group of patients that have neither thin nor thick corneas. According to this analysis, thin corneas were considered as $CT < 510$ μm and thick corneas as having $CT > 561$ μm but the results were the same as for the previous cut-off criteria of 540 μm.

Conversely, IOP_c did not display such a dependency on central corneal thickness. This result is expected

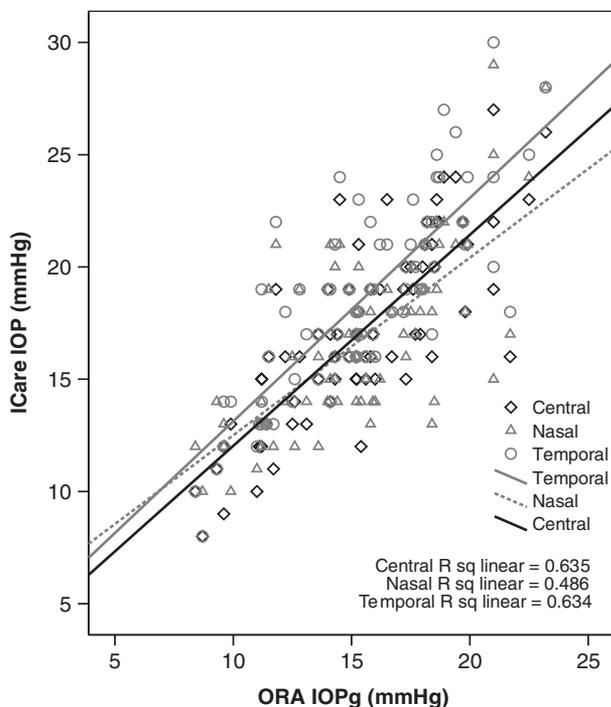
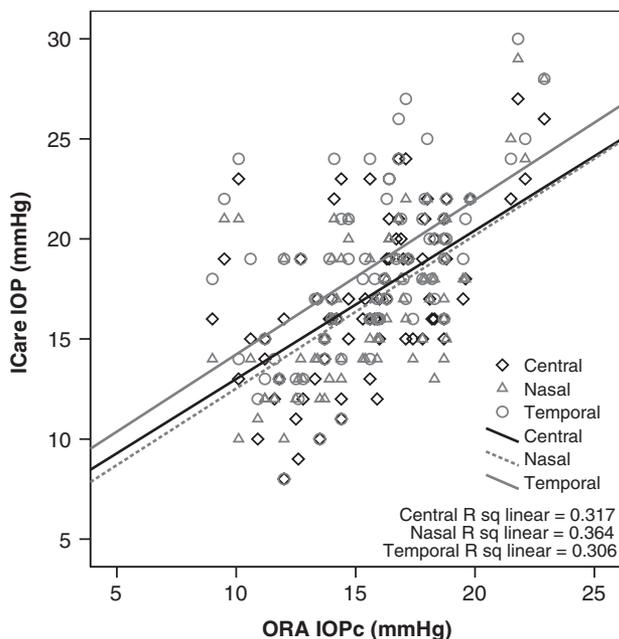


FIGURE 2. Relationship between ICare and ORA IOP.

because IOPc is designed to compensate for the overall biomechanical response of the cornea, in which central corneal thickness plays a role.

DISCUSSION

Regression analysis showed that ICare measures have higher correlation with biomechanical properties of the cornea as represented by the CRF (Table 2) than

TABLE 2. Significant Correlations of Biomechanical Parameters CRF and CH Obtained With the ORA With the Remaining Parameters Measured in the Study

	Correlation Coefficient	Statistical Significance (2-tailed)
CRF vs.		
CH	0.779*	$P < 0.001$
IC _c	0.699*	$P < 0.001$
IC _n	0.489*	$P < 0.001$
IC _t	0.702*	$P < 0.001$
CT _c	0.696*	$P < 0.001$
CT _n	0.627*	$P < 0.001$
CT _t	0.629*	$P < 0.001$
CH vs.		
IC _c	0.287*	$P = 0.012$
IC _n	0.078*	NS
IC _t	0.358†	$P = 0.002$
CT _c	0.609†	$P < 0.001$
CT _n	0.519†	$P < 0.001$
CT _t	0.567†	$P < 0.001$

n = 76.

*Spearman coefficient (nonparametric correlation).

†Pearson coefficient (parametric correlation).

corneal thickness itself (Table 3). Previous studies have also reported a trend for ICare IOP overestimation in thicker corneas.¹⁸ However, to the best of our knowledge, this is the first study analyzing the central and peripheral correlations between ICare IOP and corneal thickness with the corneal biomechanical properties.

CH and corneal thickness demonstrated a much higher correlation than in previous studies.⁵ However, CH did not demonstrate a correlation with ICare readings as high as did CRF, but a significant correlation was still found between CH and ICare IOP measured in the temporal cornea. CH is a function of the energy absorbed by the corneal tissue during applanation and relaxation. Energy absorption could also affect the measurement with the ICare tonometer as this measurement correlates with the inverse of the probe's deceleration speed after the impact with the cornea. This could explain the relationship obtained between ICare IOP and CRF, and at a lower level with CH. This relationship was not present with Goldmann tonometry where a contact method, not impact as in rebound tonometry, is used to obtain the measurement. Theoretically, a cornea with higher values of CH would display a longer delay in response to stress and relaxation forces, which indirectly means that it absorbs more energy when the air-puff is directed towards its tissue. For an impact based method of IOP measurement, this would mean that the higher the CH, the higher the ICare reading would be assuming that a higher amount of energy absorbed by the cornea would induce a more rapid deceleration in the tip displacement. This is in fact the trend we have found in the present study. On the other hand, less attention has been paid to the ORA's CRF.

According to the ORA's inventor, CH is more directly linked to the elastic properties of the cornea whereas the CRF is a measurement of the cumulative

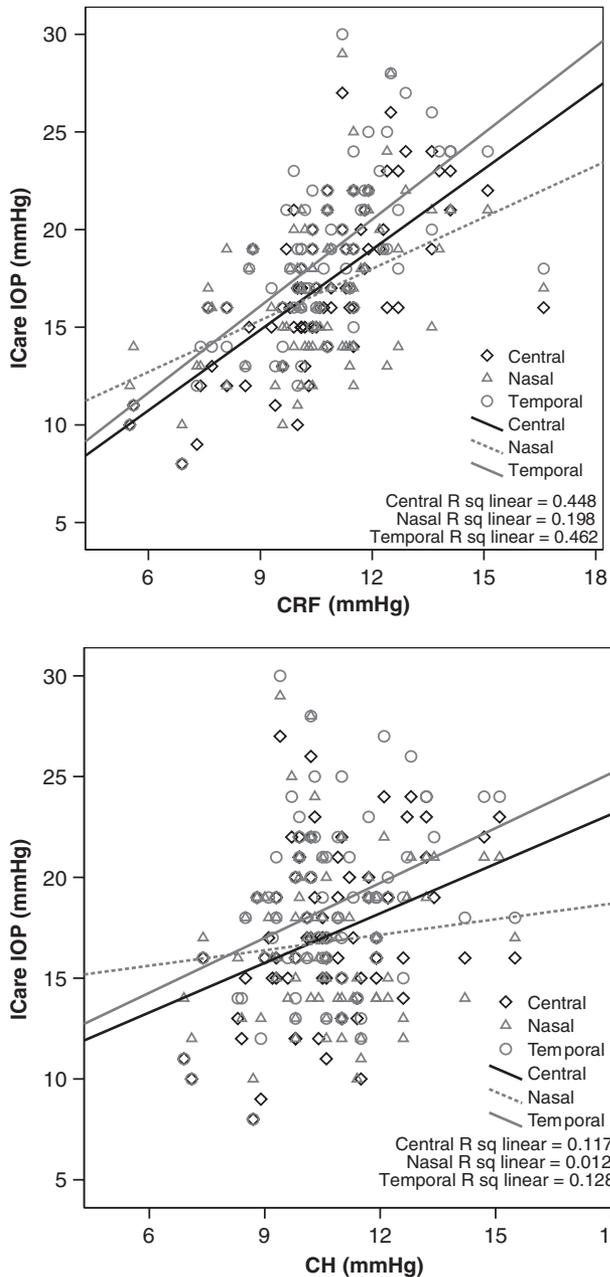


FIGURE 3. Regression analysis of IOP obtained with ICare at different corneal locations and CRF measured with ORA.

effects of viscous and elastic resistance encountered by the air-puff during the aplanation of the corneal surface.^{7,9} Regarding to the correlation with IOP, CRF is positively related with IOP, increasing at significantly elevated pressures. Conversely, no change or a slight decrease in CH has been documented for higher IOP values. The highly significant positive correlation between ICare readings and CRF could indicate that ICare readings are affected by other corneal properties and not only by corneal viscous properties. However, the isolated impact of corneal thickness, elastic and viscous tissue properties

TABLE 3. Significant Correlations of IOP Values Obtained With the ICare Rebound Tonometer With the Remaining Parameters Measured in the Study

	Correlation Coefficient	Statistical Significance (2-tailed)
IC _c vs.		
CT _c	0.466*	P < 0.001
CT _n	0.417*	P < 0.001
CT _t	0.419*	P < 0.001
IC _n vs.		
CT _c	0.167*	NS
CT _n	0.245*	P = 0.034
CT _t	0.154*	NS
IC _t vs.		
CT _c	0.476†	P < 0.001
CT _n	0.459†	P < 0.001
CT _t	0.419†	P < 0.001

Correlations among ICare readings are not displayed but they are statistically significant. Correlations between ICare measurements and biomechanical properties of the cornea have been presented in Table 2.

n = 76.

*Spearman coefficient (nonparametric correlation).

†Pearson coefficient (parametric correlation).

in IOP values obtained by rebound tonometry and other methods is presently unknown.

The stronger correlation found in the present study between ICare IOP values and Goldmann (GAT) equivalent IOP value (IOPg) agrees with previous studies on the relationships between conventional and portable GAT with ICare.^{16,17} Conversely, the lower correlation found when ICare IOP values were correlated to IOP compensated for the corneal properties (IOPc) suggests that ICare readings are affected by corneal properties and not only by the actual IOP of the eye. The higher correlation of IOP with biomechanical properties than corneal thickness agrees with the theories postulated by previous investigators,²⁴ and suggests that corneal response to stress and relaxation forces during tonometric measurements is much more complex than an anatomical question related to corneal thickness changes.^{5,25}

In previous experiments conducted at our group, we were unable to find a consistent relationship between IOP values measured with the rebound tonometer and increased peripheral corneal thickness in normal corneas^{10,11}; in fact 80% of the eyes displayed peripheral values within ± 1 mm Hg of the central reading. Moreover, in many situations, we could even obtain higher values of IOP within the thinner central cornea than at thicker corneal periphery. Similar results were obtained in the present sample. In another study, comprising a larger number of patients within a wide range of ages, we had observed that ICare readings decreased with age, and this decrease was significant for peripheral readings.¹⁰ In this study, we were not able to reproduce the results obtained previously. However, the spectrum of age is significantly more limited in this occasion. Considering all data presently available, we can conclude that the ICare rebound tonometer is not sensitive to increased peripheral corneal thickness as previously measured in other

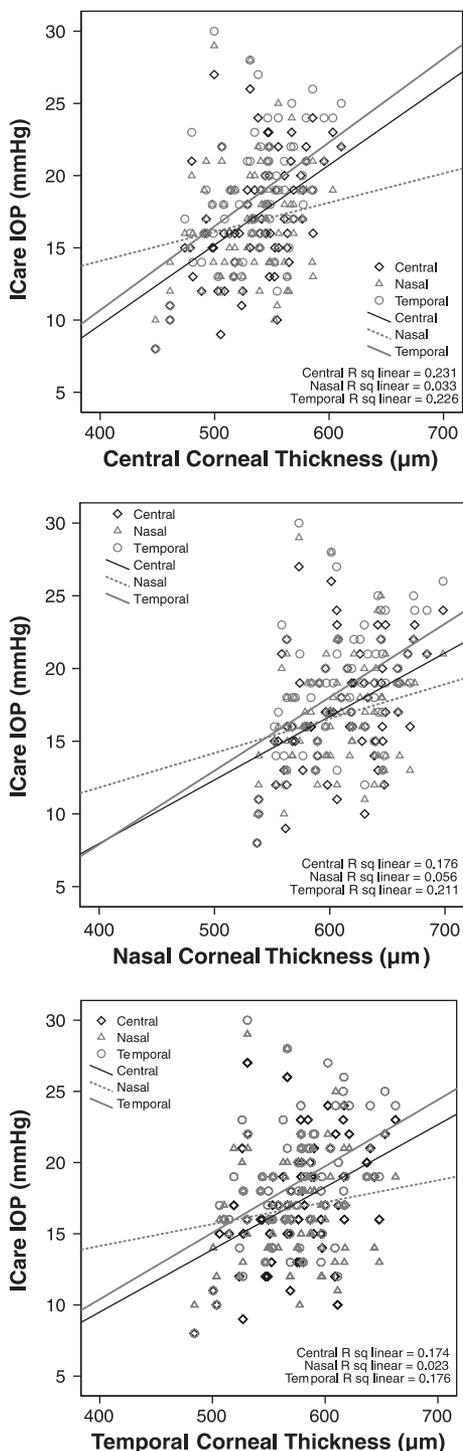


FIGURE 4. Regression analysis of IOP obtained with ICare at different corneal locations against corneal thickness.

studies^{10,11}; but at the same time thicker corneas have, on average, higher IOP values with the same instrument. We could hypothesize that for a certain cornea, with its particular physiologic, histologic, and microstructural

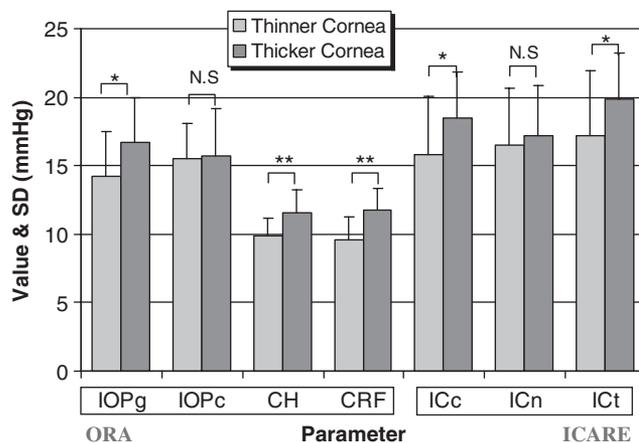


FIGURE 5. Comparison of tonometry and biomechanical properties for thinner ($\leq 540 \mu\text{m}$) and thicker corneas ($> 540 \mu\text{m}$). NS indicates nonsignificant; * $P < 0.05$; ** $P < 0.001$.

characteristics, a significant increase in thickness in the periphery does not cause a significantly different response to the impact of the ICare tonometer. We believe that “individual physiologic variations in corneal material properties (the elastic and viscoelastic responses) may be a more important determinant of corneal structural response than corneal thickness.” This is consistent with the arising common thought that complex relationships between corneal thickness and biomechanical properties of the cornea could affect the IOP readings.

To elucidate the potential effect of corneal properties other than corneal thickness in rebound tonometry, further investigations should be carried out involving patients affected of different corneal conditions as keratoconus, corneal thinning because of refractive surgery, or chronic corneal edema.

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