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ORIGINAL PAPER

The influence of corneal geometrical and biomechanical properties on tonometry readings in keratoconic eyes

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Abstract

Purpose To identify the effect of corneal geometrical and biomechanical parameters on the intraocular pressure (IOP) measurements obtained by Goldmann Applanation Tonometer (GAT), non-contact tonometer, iCare Pro Rebound Tonometer (IRT), Tonopen and Ocular Response Analyzer (ORA, Goldmann-correlated IOP: IOPg, corneal compensated IOP: IOPcc).

Methods We prospectively recruited patients with a tomographically confirmed diagnosis of keratoconus. IOP measurements were performed in the following order: non-contact tonometry, ORA, IRT, GAT and Tonopen. The means of the three IOP measurements were used for the analysis. Correlation analyses were performed to assess the association between tonometer readings and the corneal geometrical and biomechanical parameters including ORA waveform parameters. Tonometer variability was assessed using a stepwise linear regression analysis.

Results Fifty-one patients with keratoconus (27 females, mean age 30.8 ± 8.7 years) were evaluated. The highest mean IOP was measured by IOPcc (14.6 ± 2.3 mmHg) followed by IRT IOP (13.0 ± 3.2 mmHg), Tonopen IOP 12.0 ± 2.6 mmHg), GAT IOP (11.7 ± 3.1 mmHg), NCT IOP (10.2 ± 3.2 mmHg) and IOPg (10.2 ± 3.6 mmHg). NCT and IOPg were affected from all corneal parameters including thickness, curvature and biomechanical parameters. While GAT and IRT had significant correlations with corneal resistance factor (CRF) and corneal hysteresis, IOPcc only had a significant correlation with CRF. None of the corneal factors had any statistically significant correlation with Tonopen. CRF predicted tonometer measurement variability in 7 of the 15 inter-device variability assessments.

Conclusion Tonopen was the least affected from the corneal parameters followed by IOPcc and GAT. CRF was a strong determinant of tonometer variability.

Keywords Keratoconus · Corneal biomechanics · Intraocular pressure · Tonometry

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Introduction

Keratoconus is characterized by conical protrusion of the cornea with progressive corneal thinning and biomechanical instability [1, 2]. Although keratoconus patients generally exhibit low intraocular pressure (IOP) values [3–5], the risk of glaucoma is not entirely absent as a possible relationship between keratoconus and normal-tension glaucoma has been previously reported [6]. Thus, measurement of IOP remains a vital element in diagnosing and monitoring patients with coexistent keratoconus and glaucoma.

Conventional IOP measurement systems induce mechanical changes in the cornea from which they indirectly derive the pressure inside the eyeball based on certain assumptions. However, it is well known that these assumptions may not be valid due to significant variations in corneal thickness and curvature over the corneal surface in keratoconic eyes. Furthermore, techniques that involve corneal applanation may also be affected by focal irregularities in corneal geometrical and biomechanical properties given that these devices sample a very limited area on the cornea.

Measurement of IOP in keratoconus patients is challenging due to the influence of various corneal geometrical and biomechanical factors on the readings. More importantly, progression of keratoconus may result in significant geometrical and biomechanical alterations leading to potential IOP measurement errors. Furthermore, contrary to previous assumptions, findings of recent in vitro and in vivo studies in keratoconus eyes point out to the focal nature of biomechanical weakening with normal biomechanical properties outside the cone area [7–9]. These features further compound the difficulties encountered with IOP measurement in patients with keratoconus.

It is clear from the reported inter-device inconsistencies that different tonometers should not be used interchangeably in keratoconus patients [10–13]. However, the significant influence of various corneal properties on the IOP measurements entails the question of whether focal changes over time in an individual, namely keratoconus progression, would cause erroneous IOP measurements even though the same tonometer is used longitudinally in monitoring IOP. Accordingly, a tonometry method that is least affected by corneal properties would be expected to cause fewer measurement errors over time in a potentially progressive disease. In this study, we assessed the effect of various corneal geometrical and biomechanical parameters including Ocular Response Analyzer (ORA) waveform-derived parameters on the IOP measurements obtained by Goldmann Applanation Tonometer (GAT), non-contact tonometer, iCare Pro Rebound Tonometer (IRT), Tonopen and ORA.

Materials and methods

This cross-sectional study was approved by the Clinical Research Ethical Board of the Eskisehir Osmangazi University and was conducted in adherence to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the patients.

Patients with an established diagnosis of keratoconus were prospectively recruited from the cornea clinics of the Eskisehir Osmangazi University Hospital. The diagnosis of keratoconus was based on the following findings: biomicroscopic signs such as Fleischer ring, Vogt Striae and apical scarring; keratometry values ($K1/K2$) $> 48D$, maximum keratometry (K_{max}) $> 49D$; and corneal tomographical findings compatible with keratoconus such as large irregular astigmatism, abnormal posterior elevation and corneal thickness distribution. Patients were excluded if they wore contact lenses within the week prior to enrollment or had a poor ORA waveform score (< 5.0) with distorted inward and outward applanation infrared (IR) signals, glaucoma, previous corneal hydrops, active ocular surface disease, corneal epithelial defects and had undergone ocular surgery including cross-linking. Patients underwent a standardized ophthalmologic examination which included automated refraction (Tonoref II tonometer–refractometer; Nidek Co., Ltd., Gamagori, Japan), visual acuity assessment, slit-lamp biomicroscopy, Pentacam HR (Oculus; Optikgeräte GmbH, Wetzlar, Germany) imaging followed by IOP measurements.

Intraocular pressure measurements were performed in the identical following order during the morning session of the clinics (09:00–12:00) to minimize the effect of diurnal variations: non-contact tonometry (Tonoref II tonometer–refractometer; Nidek Co., Ltd., Gamagori, Japan), ORA (Reichert Ophthalmic Instruments, Buffalo, NY, USA, hardware version 2.11, software version 4.12), iCare Pro (Tiolat Oy, Helsinki, Finland), GAT (Haag-Streit, Koniz, Switzerland) and

Tonopen XL (Reichert Ophthalmic Instruments). To avoid the order effect and the potential IOP reducing effects of contact methods, applanation methods were performed lastly and a 1 min and approximately 15 min recovery times were given between successive measurements performed with the same and different tonometers, respectively. Each tonometry was operated by a different observer with each observer being masked to the IOP readings obtained by other tonometers. For each tonometer, three consecutive measurements were obtained, and mean results were used for the analysis. ORA measurement with the best waveform score was considered for the analysis as recommended by the manufacturer.

The ORA is an air-pulse tonometer that evaluates IOP in adjusted forms (corneal compensated IOP [IOPcc], Goldmann-correlated IOP [IOPg]) along with two corneal biomechanical properties (corneal resistance factor [CRF] and corneal hysteresis [CH]). A software update in 2009 (version 2.0) introduced 37 new variables derived from the non-smoothed infrared signal and has been termed waveform parameters. The first set of parameters with a single number annotation describe the upper 75% of the peak height (p1area, p2area, h1, h2, w1, w2, aspect1, aspect2, uslope1, uslope2 dslope1, dslope2, slew1, slew2, mslew1, mslew2, path1, path2, aindex, bindex, dive1, dive2, aplhf), whereas the second set with a two number annotation characterizes the upper 50% of the peak height (p1area1, p2area1, h11, h21, w11, w21, aspect11, aspect21, dslope11, dslope21, uslope11, uslope21, path11, path21).

Statistical analysis

Statistical analysis was performed using the statistical package IBM SPSS Statistics for Windows (SPSS for Windows, version 20.0; IBM SPSS, Chicago, IL). Only 1 eye per patient was selected randomly for the analysis using a computer-generated randomization list. Descriptive statistics were performed to calculate demographic characteristics of the patients. Normal distribution was assessed using the Kolmogorov–Smirnov test. Keratoconus severity was assessed using Pentacam topographical keratoconus classification (TKC): TKC 1 and 1–2 were grouped as grade I, TKC 2 and 2–3 were grouped as grade II, and TKC 3 and TKC 3–4 were grouped as grade III. Repeated measures analysis of variance (ANOVA) with Bonferroni correction was used to compare differences between IOP measurements obtained by different tonometers. The strength of the association between IOP measurements and corneal geometrical (apical corneal thickness [CT], minimum CT, corneal front astigmatism [CFA], average K [Kavg] and Kmax) and biomechanical (CRF, CH and 37 waveform parameters) parameters was assessed using Pearson's or Spearman's correlation analysis based on the normality of the data. False discovery rate method was used to correct for the effect of multiple comparisons. This method was shown to offer a better trade-off between committing a Type I or Type II error when the number of tests and hence the denominator required for Bonferroni correction is substantial [14, 15]. For the correlation analyses, the following guidelines were used: an r value of > 0.3 or < -0.3 indicated moderate correlation, whereas an r value > 0.5 or < -0.5 indicated large correlation [16]. Stepwise multiple linear regression (significance level to enter $p < 0.05$) was used to identify variables (corneal geometrical and biomechanical parameters) that predicted measurement variability between the tonometers. Variables were entered into the explanatory model based on the greatest improvement in R^2, and those variables with variance inflation factor > 5 were removed so as to diminish the effect of multicollinearity. Statistical significance was assumed at $P < 0.05$ levels.

Results

Sixty-two patients were enrolled of whom 11 were excluded due to poor-quality ORA measurement leaving a total number of 51 patients for the analysis. There were no statistically significant differences between the included and excluded patients in terms of gender (27/51 females and 8/11 females, respectively, $p = 0.195$, Fisher's exact test) and age (median 28.8 years, range 16.2–53.3 years and median 29.2 years, range 22.2–51.3 years, respectively, $p = 0.352$). Excluded patients had significantly lower IRT IOP readings (median 11.5 mmHg, range 7.7–13.3 mmHg vs. median 13.2 mmHg, range 7.3–20.2 mmHg, $p = 0.033$) and waveform scores (median 3.8, range 1.60–4.8 vs. median 6.6, range 5.0–8.8, $p < 0.001$), while the other parameters were

not statistically significantly different (Supplementary Table).

Of the included eyes, 28 (54.9%) had grade I, 17 (33.3%) had grade II, and 6 (11.8%) had grade III keratoconus. Fifteen eyes (29.4%) had mild degree of scarring as denoted by a single (+) on the Pentacam topometric/keratoconus staging screen. All cones were located within a diameter of 2 mm from the corneal apex (mean 1.11 ± 0.39 mm, range 0.45–1.94 mm). Table 1 shows the mean IOPs measured by different tonometers along with the pairwise differences between the tonometers. Among the mean IOPs, the highest was IOPcc (14.6 ± 2.3 mmHg) followed by IRT IOP (13.0 ± 3.2 mmHg), Tonopen IOP 12.0 ± 2.6 mmHg), GAT IOP (11.7 ± 3.1 mmHg), NCT IOP (10.2 ± 3.2 mmHg) and IOPg (10.2 ± 3.6 mmHg). IOPcc values were statistically significantly higher compared to IOPs obtained by other tonometers (all $p < 0.001$). While the mean NCT IOP was similar to mean IOPg ($p > 0.05$), the measurements of the two tonometers were significantly lower than the other tonometers (all $p < 0.05$). Although the mean IOP recorded by Tonopen was similar when compared to IRT and GAT (all $p > 0.05$), IRT was found to overestimate IOP when GAT was considered as reference (mean difference 1.2 mmHg, $p < 0.05$).

Figures 1 and 2 illustrate the correlations between IOPs measured by different tonometers along with their relationship with corneal geometrical and biomechanical parameters. NCT had statistically significant correlations with all the other tonometers. Although GAT, IRT, IOPg and IOPcc were correlated with each other, Tonopen only had a correlation with NCT, GAT and IRT. Regarding the influence of corneal parameters on the IOP measurements, NCT was affected from all the parameters while IOPg was correlated with all except CFA. While GAT and IRT had significant correlations with CRF and CH, IOPcc only had a significant correlation with CRF. None of the corneal factors including the waveform parameters had any statistically significant correlation with the Tonopen (Fig. 2).

The stepwise multiple linear regression analysis in Table 2 shows the corneal geometrical and biomechanical parameters that predict measurement variability between the tonometers. None of the corneal parameters predicted the variability between GAT/Tonopen and GAT/IOPcc. The influence of CRF was greatest, predicting measurement variability in 7 of the 15 inter-device variability assessments. Notably, CRF was able to explain 97% of the variability between IOPg and IOPcc and 42% of the variability between IRT and IOPg as a single predictor.

Discussion

In this cross-sectional study, IOPcc, an ORA parameter, gave the highest IOP readings, whereas the other ORA parameter IOPg gave the lowest IOP readings along with NCT (Table 1). The mean IOP measured by GAT and Tonopen was similar and followed mean IOPcc and mean IOP measured by IRT in a decreasing order. Virtually, all tonometers were correlated with each other with the exception of Tonopen showing the lack of statistically significant correlation with ORA IOP parameters (IOPg and IOPcc) (Fig. 1). Corneal

Table 1 Mean ± SD intraocular pressures obtained by different tonometers and pairwise comparisons among the tonometers

	Mean ± SD (range)	Δ NCT	Δ GAT	Δ TNP	Δ iCare Pro	Δ IOPg	Δ IOPcc
NCT	10.2 ± 3.2 (4.3–20.0)		− 1.5†	− 1.8*	− 2.7*	− 0.05	− 4.3*
GAT	11.7 ± 3.1 (6.3–20.0)	1.5†		− 0.3	− 1.2†	1.5†	− 2.8*
Tonopen	12.0 ± 2.6 (7.3–18.0)	1.8*	0.3		− 0.9	1.8†	− 2.5*
iCare Pro	13.0 ± 3.2 (7.2–20.2)	2.7*	1.2†	0.9		2.7*	− 1.6*
IOPg	10.2 ± 3.6 (2.8–22.0)	0.05	− 1.5†	− 1.8†	− 2.7*		− 4.3*
IOPcc	14.6 ± 2.3 (10.3–21.9)	4.3*	2.8*	2.5*	1.6*	4.3*	

Δ mean difference, *NCT* non-contact tonometry, *GAT* Goldmann applanation tonometry, *IOPg* Goldmann-correlated intraocular pressure (IOP), *IOPcc* corneal compensated IOP

* and † denote statistical significance at $p < 0.001$ and $p < 0.05$, respectively

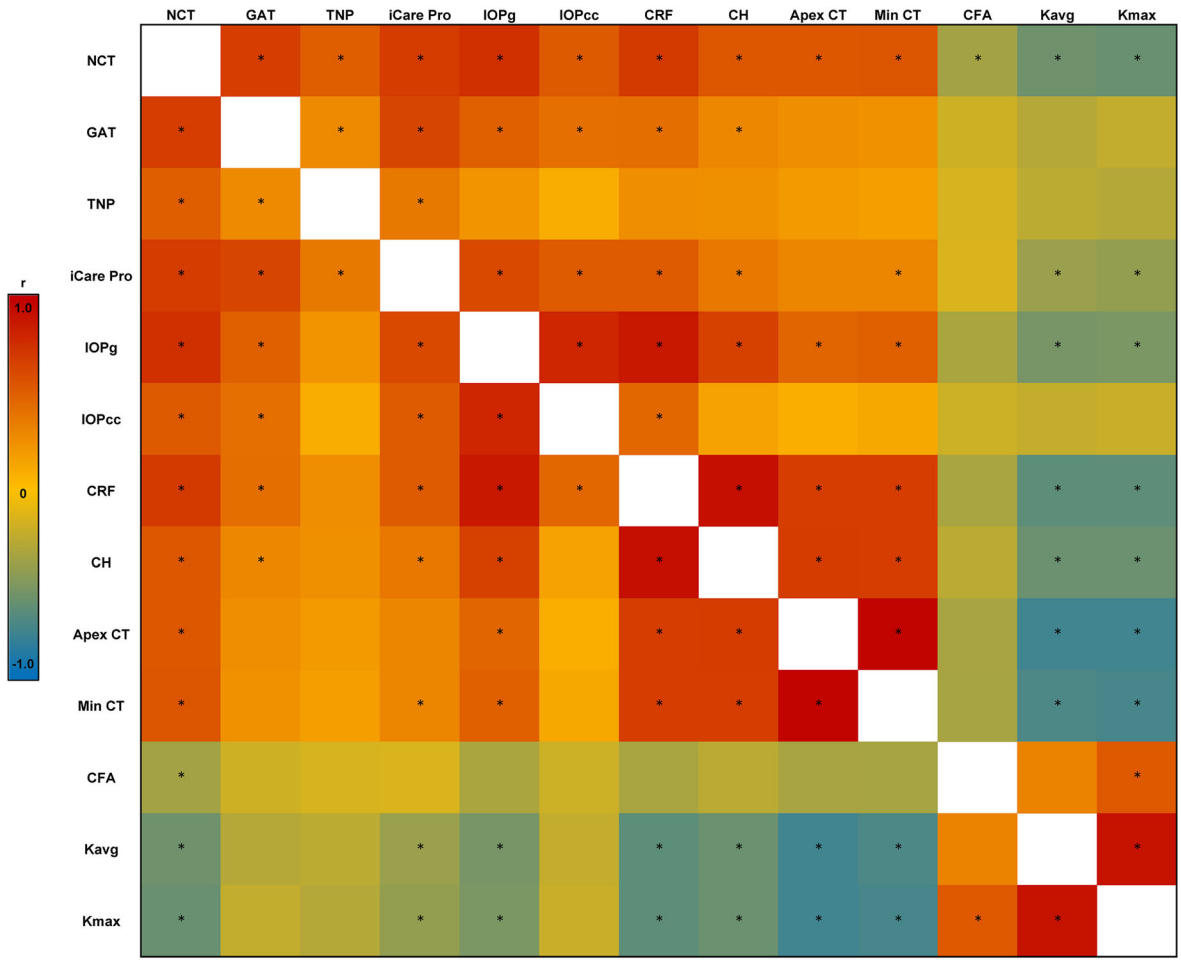

Fig. 1 Correlation matrix illustrating the linear relationship between the intraocular pressure (IOP) obtained by different tonometers and the corneal parameters. Warmer colors indicate increasing positive (uphill) linear relationship, while cooler colors indicate increasing negative (downhill) linear relationship. Cells annotated with an asterisk denote statistically significant correlations after adjusting for multiple comparisons. *NCT* non-contact tonometry, *GAT* Goldmann applanation tonometry, *TNP* Tonopen, *IOPg* Goldmann-correlated IOP, *IOPcc* corneal compensated IOP, *CRF* corneal resistance factor, *CH* corneal hysteresis, *Apex CT* apical corneal thickness, *Min CT* minimum corneal thickness, *CFA* cornea front astigmatism, K_{avg} average keratometry, K_{max} maximum keratometry

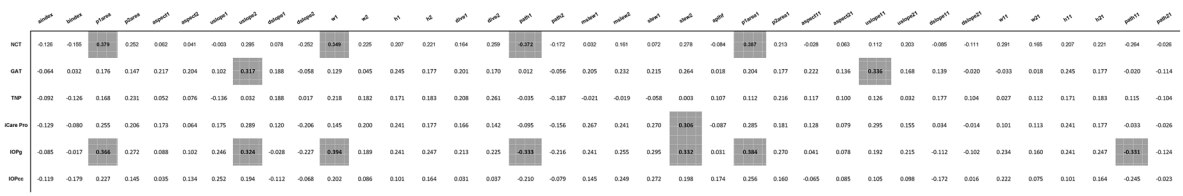

Fig. 2 Correlation analyses of the waveform parameters with the tonometers. Shaded areas indicate moderate correlations with an r value of > 0.3 or < -0.3. No statistically significant correlation was found for this analysis. *NCT* non-contact tonometry, *GAT* Goldmann applanation tonometry, *TNP* Tonopen, *IOPg* Goldmann-correlated IOP, *IOPcc* corneal compensated IOP

resistance factor and CH were observed to influence all tonometers except Tonopen. Similarly, none of the waveform parameters were found to affect Tonopen measurements (Fig. 2). Stepwise multiple linear

Table 2 Stepwise multiple linear regression analysis of tonometer variability versus corneal parameters

	No. of variables in model	Variable	β regression coefficient (95% CI)	Partial R square	Model R square
GAT/NCT	1	Path1	0.60 (0.37–0.83)*	0.35	0.35
	2	Dslope2	0.33 (0.12–0.55)†	0.10	0.45
GAT/Tonopen	No variables entered into the equation				
GAT/IRT	1	Kmax	0.31 (0.04–0.59)†	0.08	0.08
GAT/IOPg	1	CRF	− 0.59 (− 0.82 to − 0.36)*	0.34	0.34
GAT/IOPcc	No variables entered into the equation.				
NCT/TNP	1	CRF	0.58 (0.81–0.34)*	0.32	0.32
	2	Path1	− 0.34 (− 0.12 to − 0.57)†	0.10	0.42
	3	P2area	− 0.25 (− 0.007 to − 0.48)†	0.03	0.45
NCT/IRT	1	Path1	0.39 (0.12–0.66)†	0.14	0.14
NCT/IOPg	1	Uslope1	− 0.44 (− 0.18 to − 0.70)†	0.18	0.18
	2	CRF	− 0.35 (− 0.11 to − 0.59)†	0.11	0.29
	3	Kmax	− 0.40 (− 0.12 to − 0.68)†	0.09	0.38
NCT/IOPcc	1	Apex CT	0.50 (0.25–0.75)*	0.23	0.23
	2	Uslope1	− 0.39 (− 0.62 to − 0.17)†	0.14	0.37
	3	Uslope2	0.37 (0.16–0.59)†	0.12	0.49
Tonopen/IRT	1	CRF	− 0.34 (− 0.60 to − 0.06)†	0.09	0.09
Tonopen/IOPg	1	CRF	− 0.68 (− 0.89 to − 0.46)*	0.44	0.44
	2	P2area	0.23 (0.02–0.45)†	0.05	0.49
	3	Uslope1	− 0.31 (− 0.50 to − 0.12)†	0.03	0.52
	4	Dslope1	0.30 (0.11–0.49)†	0.08	0.60
	5	bindex	0.22 (0.04–0.40)†	0.04	0.64
	6	H1	− 0.50 (− 0.93 to − 0.07)†	0.03	0.67
Tonopen/IOPcc	1	Dslope1	0.30 (0.03–0.58)†	0.07	0.07
	2	Uslope1	− 0.36 (− 0.64 to − 0.09)†	0.11	0.18
IRT/IOPg	1	CRF	− 0.66 (− 0.87 to − 0.43)*	0.42	0.42
IRT/IOPcc	1	CH	0.33 (0.06–0.60)†	0.09	0.09
IOPg/IOPcc	1	CRF	0.98 (0.93–1.04)*	0.97	0.97

NCT non-contact tonometry, *GAT* Goldmann applanation tonometry, *IOPg* Goldmann-correlated intraocular pressure (IOP), *IOPcc* corneal compensated IOP, K_{max} maximum keratometry, *CRF* corneal resistance factor, *CH* corneal hysteresis, *Apex CT* apex corneal thickness

*Regression coefficient is significant at $P < 0.001$, and †regression coefficient is significant at $P < 0.05$

regression analysis did not reveal any corneal geometrical and biomechanical parameters that predicted GAT/Tonopen and GAT/IOPcc variability. Corneal resistance factor was the most frequently observed predictor of tonometer variability independently explaining 97% and 42% of IOPg/IOPcc and IRT/IOPg variability, respectively.

There is equivocal evidence in the literature regarding the effect of corneal curvature and corneal thickness on IOP readings in keratoconus patients. In this study, IOPg and NCT IOP were significantly affected by corneal thickness (Apex CT and Min CT) parameters, corneal curvature (K_{avg} and K_{max}) and corneal hysteresis (CH) (Fig. 1). On the other hand, IRT only had a statistically significant correlation with min CT. Although the majority of the work published in this field suggest no effect of corneal thickness on IOP measurements in keratoconic eyes [5, 12, 17–20], several authors have documented the contrary [10, 21–23]. Likewise, uncertainty exists regarding the effect of corneal curvature on IOP measurements with some suggesting a significant correlation

[10, 19, 23, 24], whereas the others reporting null relationship [18, 21].

In our study, CRF had a significant impact on all tonometers except Tonopen (Fig. 1). Moreover, CH was associated with GAT, IRT, NCT and IOPg, while no statistically significant correlation was observed for IOPcc. The association of CRF with IOPcc [11, 25] and IOPg [11, 25–27] as well as with the IOP measurements obtained by dynamic contour tonometry [25] and GAT [11, 25, 26] has been previously reported in keratoconus eyes. Although the effect of CCT on the IOP measurements obtained by iCare [28] and iCare Pro [22, 29] has been demonstrated in eyes with keratoconus, there is no study that has shown the effect of corneal biomechanical properties on rebound tonometry measurements in eyes with keratoconus. We have shown that IRT measurements were correlated with both CRF and CH (correlation coefficient for CRF > CH) (Fig. 1). This finding is in agreement with that of Jorge et al. [30] and Chui et al. [31] who have found a stronger correlation of rebound tonometry with CRF than CH in healthy eyes. The dependence of IRT on CRF and CH may render this IOP measurement method disadvantageous in keratoconus owing to the potential impact of focal biomechanical variations with respect to where the IRT probe hits on the cornea during the measurement. Furthermore, rebound tonometry may be more prone to incidental errors due to its very small area of contact [32]. Similar to our study, Mollan et al. have shown, in keratoconus eyes, that although CRF had an influence on GAT and IOPg, it did not affect measurements obtained by Tonopen [26]. The same study also found no influence of CH and CCT on Tonopen [26].

Corneal resistance factor has been consistently shown to perform better in distinguishing keratoconic eyes from normal eyes in the literature [27, 33, 34]. The calculation of this parameter differs only slightly from CH in that an empirically determined adjustment factor (k) is introduced into the formula (CRF = P1 − kP2) [35]. As the k is < 1.0, the result is weighted toward the first applanation event emphasizing the role of the initial elastic deformation response. In this study, CRF has been found to be the predominant parameter explaining tonometer variability in 7 of the 15 inter-device comparisons (Table 2). Corroborating with this finding, Gkika et al. have previously reported that CRF consistently predicted tonometer variability (dynamic contour tonometry, GAT and ORA) in an analysis of 50 keratoconic eyes [36]. Interestingly, although GAT/Tonopen and GAT/IOPcc variability did not have any predictors, Tonopen/IOPcc variability was in part explained by Dslope1 (downward slope) and Uslope1 (upward slope) (Table 2). This latter finding is probably due to the inverse relationship observed with these tonometers and the respective parameters. (Greater Uslope1 predicts a lower Tonopen IOP and a higher IOPcc and vice versa for Dslope1, as shown in Fig. 2.)

The importance of the first applanation in keratoconus diagnosis has also been substantiated using waveform parameters in two different studies which have reported that parameters related to the first peak, particularly p1area and p1area1, had a better discriminatory value than second peak parameters [37, 38]. A similar weighting for the first applanation has been found in this study for NCT and IOPg having significant correlations with the first applanation waveform parameters (Fig. 2). Notably Tonopen was not associated with any of the waveform parameters. These findings indicate that NCT and IOPg are expected to provide unreliable longitudinal measurements in eyes that show biomechanical alterations, namely keratoconus progression. On the contrary, Tonopen is expected to be affected least from corneal biomechanical alterations due to its lack of association with any of the ORA parameters.

There are several limitations in this study that must be considered. One limitation relates to the cross-sectional design of our study which may not hold true in a within-subject longitudinal design where the effect of changing corneal biomechanical properties on tonometers is assessed. Our sample size was relatively small increasing the likelihood of Type 2 errors, particularly for non-normally distributed waveform parameters. This was particularly evident in the correlation analyses of the waveform parameters which failed to show any statistically significant correlation possibly due to the correction applied for multiple comparisons. In order to avoid the Type 2 error inherent to numerous multiple comparisons, we nonetheless considered a correlation with an r value of at least > 0.3 or < − 0.3 as hypothetically meaningful for the waveform parameter correlation analyses. Although each tonometer was operated by a single independent observer with each observer being masked to the readings of the other tonometers, within-device measurements were done in an un-

masked fashion. Furthermore, the tonometry order was fixed with special emphasis on performing applanation methods at the end. A recovery time of approximately 15 min was allowed between different devices, but it is unknown whether the impact of a tonometer would be prolonged influencing the measurement of the subsequent tonometer. This study is also limited by not having evaluated several new biomechanical parameters that can be assessed with the new Corvis Scheimpflug Technology. Finally, we did not take into account the axis of astigmatism while measuring GAT [39]. Despite these limitations, this study is the first in evaluating the influence of ORA waveform parameters on IOP measurements in eyes with keratoconus.

Our results show that the tonometer that is least affected by the corneal geometrical and biomechanical properties evaluated in this study is Tonopen followed by ORA (IOPcc) and GAT. The Tonopen with its smaller area of contact [40] and less interference with the tear film [22] may be a better choice in a longitudinal follow-up of a patient with keratoconus. Non-contact tonometry and IOPg were found to be affected by various corneal geometrical and biomechanical parameters and were thus considered the least reliable indicators of IOP. Corneal resistance factor was the strongest determinant of tonometer variability highlighting the importance of the first applanation in corneal biomechanics. As a future direction, conducting a similar study using Corvis would be helpful in clarifying the role of corneal biomechanics on different tonometers in varying stages of keratoconus.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This cross-sectional study was approved by the Clinical Research Ethical Board of the Eskisehir Osmangazi University and was conducted in adherence to the tenets of the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Rabinowitz YS (1998) Keratoconus. Surv Ophthalmol 42(4):297–319
2. McMonnies CW, Boneham GC (2010) Corneal responses to intraocular pressure elevations in keratoconus. Cornea 29(7): 764–770. https://doi.org/10.1097/ICO.0b013e3181ca2b75
3. Bohm A, Kohlhaas M, Lerche RC, Bischoff B, Richard G (1997) Measuring intraocular pressure in keratoconus: effect of the changed biomechanics. Ophthalmologe 94(11):771–774
4. Brooks AM, Robertson IF, Mahoney AM (1984) Ocular rigidity and intraocular pressure in keratoconus. Aust J Ophthalmol 12(4):317–324
5. Patel S, McLaughlin JM (1999) Effects of central corneal thickness on measurement of intra-ocular pressure in keratoconus and post-keratoplasty. Ophthalmic Physiol Opt 19(3):236–241
6. Cohen EJ (2009) Keratoconus and normal-tension glaucoma: a study of the possible association with abnormal biomechanical properties as measured by corneal hysteresis (An AOS Thesis). Trans Am Ophthalmol Soc 107:282–299
7. Roberts CJ, Dupps WJ Jr (2014) Biomechanics of corneal ectasia and biomechanical treatments. J Cataract Refract Surg 40(6):991–998. https://doi.org/10.1016/j.jcrs.2014.04.013
8. Scarcelli G, Besner S, Pineda R, Yun SH (2014) Biomechanical characterization of keratoconus corneas ex vivo with Brillouin microscopy. Invest Ophthalmol Vis Sci 55(7):4490–4495. https://doi.org/10.1167/iovs.14-14450
9. Scarcelli G, Besner S, Pineda R, Kalout P, Yun SH (2015) In vivo biomechanical mapping of normal and keratoconus corneas. JAMA Ophthalmol 133(4):480–482. https://doi.org/10.1001/jamaophthalmol.2014.5641
10. Firat PG, Orman G, Doganay S, Demirel S (2013) Influence of corneal parameters in keratoconus on IOP readings obtained with different tonometers. Clin Exp Optom 96(2):233–237. https://doi.org/10.1111/cxo.12016
11. Goldich Y, Barkana Y, Avni I, Zadok D (2010) Goldmann applanation tonometry versus ocular response analyzer for intraocular pressure measurements in keratoconic eyes. Cornea 29(9):1011–1015. https://doi.org/10.1097/ICO.0b013e3181cda034
12. Unterlauft JD, Schadle N, Kasper K, Klink T, Geerling G (2011) Comparison of dynamic contour tonometry and Goldmann applanation tonometry in keratoconus. Cornea 30(10):1078–1082. https://doi.org/10.1097/ICO.0b013e31820cd3d6
13. Hager A, Loge K, Schroeder B, Fullhas MO, Wiegand W (2008) Effect of central corneal thickness and corneal hysteresis on tonometry as measured by dynamic contour tonometry, ocular response analyzer, and Goldmann tonometry in glaucomatous eyes. J Glaucoma 17(5):361–365. https://doi.org/10.1097/IJG.0b013e31815c3ad3

14. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B (Methodol) 57(1):289–300
15. Benjamini Y, Yekutieli D (2001) The control of the false discovery rate in multiple testing under dependency. Ann Stat 29(4):1165–1188
16. Cohen J (1988) Statistical power analysis for the behavioral sciences. In: 2nd edn. Lawrence Erlbaum, Hillsdale, NJ, p 80
17. Browning AC, Bhan A, Rotchford AP, Shah S, Dua HS (2004) The effect of corneal thickness on intraocular pressure measurement in patients with corneal pathology. Br J Ophthalmol 88(11):1395–1399. https://doi.org/10.1136/bjo.2003.037887
18. Meyenberg A, Iliev ME, Eschmann R, Frueh BE (2008) Dynamic contour tonometry in keratoconus and postkeratoplasty eyes. Cornea 27(3):305–310. https://doi.org/10.1097/ICO.0b013e31815dcf97
19. Ozbek Z, Cohen EJ, Hammersmith KM, Rapuano CJ (2006) Dynamic contour tonometry: a new way to assess intraocular pressure in ectatic corneas. Cornea 25(8):890–894. https://doi.org/10.1097/01.ico.0000224649.12214.33
20. Altinkaynak H, Kocasarac C, Dundar H, Sayin N, Kara N, Bozkurt E, Duru N (2016) Which tonometry in eyes with keratoconus? Eye (Lond) 30(3):431–437. https://doi.org/10.1038/eye.2015.248
21. Papastergiou GI, Kozobolis V, Siganos DS (2008) Assessment of the pascal dynamic contour tonometer in measuring intraocular pressure in keratoconic eyes. J Glaucoma 17(6):484–488. https://doi.org/10.1097/IJG.0b013e3181622502
22. Mendez-Hernandez C, Arribas-Pardo P, Cuina-Sardina R, Fernandez-Perez C, Mendez-Fernandez R, Saenz-Frances F, Benitez-Del-Castillo JM, Garcia-Feijoo J (2017) Measuring intraocular pressure in patients with keratoconus with and without intrastromal corneal ring segments. J Glaucoma 26(1):71–76. https://doi.org/10.1097/IJG.0000000000000549
23. Cairns R, Graham K, O'Gallagher M, Jackson AJ (2018) Intraocular pressure (IOP) measurements in keratoconic patients: do variations in IOP respect variations in corneal thickness and corneal curvature? Cont Lens Anterior Eye. https://doi.org/10.1016/j.clae.2018.11.007
24. Read SA, Collins MJ (2011) Intraocular pressure in keratoconus. Acta Ophthalmol 89(4):358–364. https://doi.org/10.1111/j.1755-3768.2009.01690.x
25. Bayer A, Sahin A, Hurmeric V, Ozge G (2010) Intraocular pressure values obtained by ocular response analyzer, dynamic contour tonometry, and Goldmann tonometry in keratokonic corneas. J Glaucoma 19(8):540–545. https://doi.org/10.1097/IJG.0b013e3181ca7aeb
26. Mollan SP, Wolffsohn JS, Nessim M, Laiquzzaman M, Sivakumar S, Hartley S, Shah S (2008) Accuracy of Goldmann, ocular response analyser, Pascal and TonoPen XL tonometry in keratoconic and normal eyes. Br J Ophthalmol 92(12):1661–1665. https://doi.org/10.1136/bjo.2007.136473
27. Touboul D, Roberts C, Kerautret J, Garra C, Maurice-Tison S, Saubusse E, Colin J (2008) Correlations between corneal hysteresis, intraocular pressure, and corneal central pachymetry. J Cataract Refract Surg 34(4):616–622. https://doi.org/10.1016/j.jcrs.2007.11.051
28. Ozcura F, Yildirim N, Tambova E, Sahin A (2017) Evaluation of Goldmann applanation tonometry, rebound tonometry and dynamic contour tonometry in keratoconus. J Optom 10(2):117–122. https://doi.org/10.1016/j.optom.2016.04.005
29. Smedowski A, Weglarz B, Tarnawska D, Kaarniranta K, Wylegala E (2014) Comparison of three intraocular pressure measurement methods including biomechanical properties of the cornea. Invest Ophthalmol Vis Sci 55(2):666–673. https://doi.org/10.1167/iovs.13-13172
30. Jorge JM, Gonzalez-Meijome JM, Queiros A, Fernandes P, Parafita MA (2008) Correlations between corneal biomechanical properties measured with the ocular response analyzer and ICare rebound tonometry. J Glaucoma 17(6):442–448. https://doi.org/10.1097/IJG.0b013e31815f52b8
31. Chui WS, Lam A, Chen D, Chiu R (2008) The influence of corneal properties on rebound tonometry. Ophthalmology 115(1):80–84. https://doi.org/10.1016/j.ophtha.2007.03.061
32. Rosentreter A, Athanasopoulos A, Schild AM, Lappas A, Cursiefen C, Dietlein TS (2013) Rebound, applanation, and dynamic contour tonometry in pathologic corneas. Cornea 32(3):313–318. https://doi.org/10.1097/ICO.0b013e318254a3fb
33. Mikielewicz M, Kotliar K, Barraquer RI, Michael R (2011) Air-pulse corneal applanation signal curve parameters for the characterisation of keratoconus. Br J Ophthalmol 95(6):793–798. https://doi.org/10.1136/bjo.2010.188300
34. Schweitzer C, Roberts CJ, Mahmoud AM, Colin J, Maurice-Tison S, Kerautret J (2010) Screening of forme fruste keratoconus with the ocular response analyzer. Invest Ophthalmol Vis Sci 51(5):2403–2410. https://doi.org/10.1167/iovs.09-3689
35. De Stefano VS, Dupps WJ Jr (2017) Biomechanical diagnostics of the cornea. Int Ophthalmol Clin 57(3):75–86. https://doi.org/10.1097/IIO.0000000000000172
36. Gkika MG, Labiris G, Kozobolis VP (2012) Tonometry in keratoconic eyes before and after riboflavin/UVA corneal collagen crosslinking using three different tonometers. Eur J Ophthalmol 22(2):142–152. https://doi.org/10.5301/EJO.2011.8328
37. Luz A, Lopes B, Hallahan KM, Valbon B, Ramos I, Faria-Correia F, Schor P, Dupps WJ Jr, Ambrosio R Jr (2016) Enhanced combined tomography and biomechanics data for distinguishing forme fruste keratoconus. J Refract Surg 32(7):479–494. https://doi.org/10.3928/1081597X-20160502-02
38. Wolffsohn JS, Safeen S, Shah S, Laiquzzaman M (2012) Changes of corneal biomechanics with keratoconus. Cornea 31(8):849–854. https://doi.org/10.1097/ICO.0b013e318243e42d
39. Mark HH, Mark TL (2003) Corneal astigmatism in applanation tonometry. Eye (Lond) 17(5):617–618. https://doi.org/10.1038/sj.eye.6700417
40. Mok KH, Wong CS, Lee VW (1999) Tono-Pen tonometer and corneal thickness. Eye (Lond) 13(Pt 1):35–37. https://doi.org/10.1038/eye.1999.7

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