Repeatability of the Pentacam HR in Various Grades of Keratoconus

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• PURPOSE: To evaluate the repeatability of an extensive number of relevant indices with the Pentacam HR in keratoconus of varying severity and normal eyes.
• DESIGN: Reliability analysis.
• METHODS: This study was performed at Antwerp University Hospital, Belgium, and enrolled 20 healthy volunteers (20 eyes) and 69 patients (69 eyes) with keratoconus. Three consecutive measurements were performed by the same operator with Pentacam HR in keratoconus and normal eyes. Exclusion criteria included past ocular surgery, recent rigid contact lens wear, and corneal scarring. The keratoconus group was subdivided according to the Belin/Ambrosio total deviation value: subclinical, mild, and moderate. The within-subject standard deviation and repeatability limit were computed for repeatability assessment. The tolerance index (TI) was calculated to compare across parameters with different measurement scales. For the sample size included, TI $>$ 0.36 signified statistical significance at the 0.05 level.
• RESULTS: Repeatability in subclinical keratoconus did not differ significantly from controls ($P > .05$), except for wavefront aberrations. In mild keratoconus, 11 of 18 (61.1%) anterior corneal, 7 of 14 (50%) posterior corneal, 2 of 5 (40%) pachymetry, 7 of 11 (63.6%) combined, and 1 of 6 (16.7%) densitometry parameters showed significantly worse repeatability compared to controls (TI $>$ 0.36). Repeatability of most parameters worsened in moderate disease. In particular, maximal keratometry and anterior astigmatism showed significantly worse repeatability in moderate keratoconus.
• CONCLUSIONS: Measurement variability of Pentacam HR is of clinical relevance when assessing for progression of keratoconus. We provide reference repeatability values and scale independent analysis of relevant corneal parameters in keratoconus of varying degrees. (Am J Ophthalmol 2020;219:154–162.

CORNEAL IMAGING TECHNIQUES HAVE EVOLVED into an invaluable tool in both diagnosis and management of keratoconus. Corneal cross-linking, a treatment designed to arrest progression of keratoconus, is generally indicated following detection of progressive disease.[1] Studies examining the precision of corneal imaging devices are required to elucidate how likely a measured change reflects real change in keratoconus. The variation of a measurement system can be split into 2 components: repeatability and reproducibility. Repeatability, or test-retest reliability, is the variability in measurements taken under stable conditions by a single examiner, within a short period of time over which the underlying value is considered to remain constant.[2] Reproducibility refers to the variability in repeated measurements made on a subject under changing conditions, for instance another observer.[2]

Reports have demonstrated the excellent repeatability of measurements taken with the Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany) in healthy eyes.[3,4] Repeatability of this device is known to be reduced in keratoconus, but to date, reports on this subject have assessed a limited number of parameters in either a narrow range of keratoconus severity or mixed groups of varying severity.[5–12] The Pentacam software does not include reference data on the measurement noise of specific parameters such as the commonly used maximal keratometry (K_{max}), with the exception of the ABCD progression display. This keratoconus-specific grading system assesses the anterior corneal curvature (A), posterior corneal curvature (back surface, B), corneal pachymetry at thinnest (C), and distance best-corrected vision (D), with an additional modifier for the level of scarring.[13] For both the normal and keratoconic population, 80% and 95% confidence intervals for the components of the ABCD classification are provided on the progression display of the Pentacam for comparison of serial measurements in an individual patient.[12] Proper quantification of measurement variability of relevant corneal parameters in different stages of the disease is vital to the judicious use of corneal cross-linking. If changes in serial measurements are the result of poor repeatability rather than actual progression, patients may receive unnecessary cross-linking treatment. The present study aims to investigate the

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intra-examiner repeatability of the Pentacam in measuring keratoconus of varying severity for an extensive number of clinically relevant parameters, including the components of the ABCD classification. This will aid clinicians in selecting adequate parameters and threshold values for progression analysis.

METHODS

THIS RELIABILITY ANALYSIS WAS CARRIED OUT AT Antwerp University Hospital, Belgium, with the approval of the institutional ethics committee. Written informed consent was obtained from all patients prior to the start of the study. Eyes of previously diagnosed keratoconus patients (n = 69 patients) (keratoconus group) and healthy volunteers (n = 20) (control group) were examined using the Pentacam. Patients with a history of ocular surgery or corneal scarring were excluded.

The Pentacam uses a monochromatic blue light-emitting diode with a wavelength of 475 nm and a Scheimpflug camera that rotates around the corneal axis. Participants were asked to blink before each scan was taken, open both eyes, and stare at the central fixation light. Three measurements were taken per eye in scotopic conditions by a single operator using the standard resolution (25 images in 2 seconds). Only scans with a quality specification of "OK" were taken for analysis; low-quality scans were deleted, and the measurements repeated. For statistical analysis, data from 1 eye of patients with bilateral disease were included by computerized random number selection. Some parameters, such as Zernike polynomials, are subject to left-right symmetry. It does not pose an issue in this study, as the repeatability rather than the actual value is of importance. Keratoconus diagnosis was based on slit-lamp findings (including stromal thinning, iron line at the base of the cone, and Vogt striae) and associated characteristic tomographic patterns. The control group consisted of 20 healthy volunteers recruited from the staff of Antwerp University Hospital. Exclusion criteria were the following: recent rigid contact lens wear, a history of ocular surgery, and a degree of ametropia greater than ±10 diopters (D). One eye per participant was selected by computerized random number selection. Eyes were stratified based on the Belin/Ambrosio enhanced ectasia total deviation value (BAD-D index), as several studies have shown it to be a strong parameter to differentiate both keratoconus and subclinical keratoconus from normal corneas.[14,15] Three groups were defined as follows, based on the Pentacam cut-off values: normal: BAD-D <1.6 (n = 22); subclinical keratoconus: BAD-D ≥1.6 and <3.0 (n = 17); mild keratoconus: BAD-D ≥3.0 and <7.0 (n = 24); moderate keratoconus: BAD-D ≥7.0 (n = 26).

The cut-off values of 1.6 and 3.0 for BAD-D are provided by the Pentacam software to distinguish normal, suspect, and keratoconus eyes, respectively. A cut-off value of 7.0 was selected by investigator consensus to differentiate mild from moderate keratoconus, as this value resulted in groups of equivalent size and the cut-off value coincided with ±50 D K_{max}. The latter group is referred to as "moderate" rather than severe/advanced, as it does not include very steep corneas (with K_{max} >70 D; K_{max} range is 50.3-69.5 D).

A large number of corneal parameters were investigated that were of potential interest in keratoconus follow-up, including parameters used for progression analysis in cross-linking trials and recently described keratoconus indices. Relevant corneal parameters were grouped as being associated with the anterior corneal surface, posterior corneal surface, corneal thickness, or a combination of these, as proposed in the Global Consensus guidelines.[1] As per current guidelines from the British and International Standards, repeated-measures analysis of variance was performed to determine the within-subject standard deviation (S_w). The S_w is the repeatability of the measurements. The repeatability limit or "repeatability coefficient" r represents the likely limits within which 95% of the measurements occur and is calculated by $S_w \times 1.96 \times \sqrt{2}$, as recommended by Bland and Altman.[16] To allow comparison of repeatability across parameters with different measurement scales (eg, μm, D), the tolerance index (TI) was calculated using the following formula:[17] $TI = \log (r_P/r_C)$ With r_P being the r in pathologic eyes and r_C being the r in healthy controls. This scale-independent index reflects whether repeatability of a parameter is significantly different in 2 samples (eg, pathologic eyes vs healthy eyes). The TI in subclinical, mild, and moderate keratoconus was calculated compared to the control group. In order to highlight parameters particularly susceptible to worsening repeatability in more advanced keratoconus, TI was also calculated comparing moderate to mild keratoconus (relative index [RI]). With the sample sizes included in this study, a TI value of >0.36 indicates that confidence limits do not overlap and there is a statistically significant difference at the 5% level ($P < .05$).[17] Data were directly exported from the Pentacam to spreadsheets in Excel (version 16.16.10; Microsoft Corp, Redmond, Washington, USA) and analyzed using XLSTAT (Version 2019.1.3; Addinsoft, Paris, France).

RESULTS

THE IMAGES OF 69 EYES OF 69 PREVIOUSLY DIAGNOSED KERATOconus patients (35 right and 34 left eyes) and 20 eyes of 20 healthy controls (10 right and 10 left eyes) were analyzed and stratified using the BAD-D index. The mean age of the keratoconus group and the control group was 34 ± 9.4 years and 31.9 ± 9.6 years, respectively.

TABLE 1. Overview of Repeatability Findings in Normal and Keratoconus Eyes for Anterior and Posterior Corneal Parameters

	Normal (N = 22)			Subclinical Keratoconus (N = 17)				Mild Keratoconus (N = 24)				Moderate Keratoconus (N = 26)				
	Mean ± SD	S_w	r	Mean ± SD	S_w	r	TI[a]	Mean ± SD	S_w	r	TI[a]	Mean ± SD	S_w	r	TI[a]	RI[a]
Anterior																
K1 (D)	42.4 ± 1.0	0.06	0.16	43.1 ± 1.6	0.07	0.18	0.07	42.9 ± 1.8	0.23	0.63	0.61*	45.7 ± 3.7	0.31	0.87	0.74*	0.14
K2 (D)	43.2 ± 0.9	0.07	0.2	44 ± 1.4	0.07	0.18	−0.04	45.3 ± 1.5	0.21	0.57	0.46*	49.2 ± 3.7	0.3	0.82	0.61*	0.16
Km (D)	42.8 ± 0.9	0.06	0.15	43.6 ± 1.5	0.06	0.16	0.01	44.1 ± 1.6	0.20	0.57	0.57*	47.4 ± 3.6	0.24	0.66	0.64*	0.07
Astig (D)	0.9 ± 0.6	0.06	0.16	0.5 ± 1.1	0.09	0.25	0.2	2.4 ± 1.1	0.14	0.4	0.4*	3.5 ± 1.7	0.38	1.05	0.82*	0.42*
K_{max} (D)	43.7 ± 1	0.17	0.47	45 ± 1.3	0.09	0.25	−0.28	48.8 ± 2.4	0.22	0.61	0.11	56.5 ± 4.5	0.6	1.66	0.55*	0.44*
Zonal K_{max} (3 mm)	43.2 ± 0.9	0.11	0.29	44.5 ± 1.2	0.09	0.24	−0.08	47.4 ± 2.2	0.2	0.55	0.28	53.7 ± 3.3	0.26	0.71	0.38*	0.11
Zonal K_{max} (4 mm)	43.1 ± 0.9	0.1	0.27	44.5 ± 1.2	0.09	0.24	−0.05	47.2 ± 2.1	0.18	0.49	0.26	53.3 ± 3.3	0.24	0.67	0.4*	0.14
Zonal K_{max} (5 mm)	43 ± 0.9	0.09	0.26	44.3 ± 1.2	0.1	0.28	0.02	46.9 ± 2	0.18	0.51	0.29	52.6 ± 3.1	0.22	0.61	0.36*	0.07
BFS (mm)	8 ± 0.2	0.01	0.02	7.9 ± 0.3	0.01	0.03	0.1	7.8 ± 0.3	0.02	0.04	0.25	7.5 ± 0.4	0.02	0.05	0.32	0.08
AE (μm)	4.1 ± 2.3	0.44	1.23	6.3 ± 3.6	0.71	1.98	0.21	16.6 ± 7.7	1.1	3.05	0.39*	34 ± 9	0.89	2.47	0.3	−0.09
ARC (mm)	7.9 ± 0.2	0.01	0.04	7.7 ± 0.2	0.01	0.04	0.01	7.3 ± 0.3	0.04	0.11	0.45*	6.6 ± 0.4	0.06	0.16	0.61*	0.16
A score	0 ± 0	0	0	0.2 ± 0.3	0.03	0.1	–[b]	0.97 ± 0.7	0.14	0.38	–[b]	3 ± 1.4	0.19	0.54	–[b]	0.16
RMS (total)	174.4 ± 10	0.41	1.15	182 ± 17.5	3.7	10.3	0.95*	187 ± 16	3.57	9.9	0.94*	193.8 ± 21	12.3	34.1	1.47*	0.54*
RMS (HOA)	2.5 ± 2.6	0.1	0.29	5.1 ± 5	0.85	2.36	0.91*	6.6 ± 3.7	0.81	2.23	0.89*	9.2 ± 4.4	1.95	5.41	1.27*	0.38*
Z (2,2)	−3.1 ± 4.4	1.13	3.14	−8.8 ± 10	1.47	4.08	0.11	−10.2 ± 12	2.04	5.64	0.25	−12.8 ± 13	3.48	9.65	0.49*	0.23
Z (2,0)	184.4 ± 28	0.91	2.53	216 ± 25.3	3.76	10.43	0.61*	230 ± 21	3.75	10.4	0.61*	234 ± 27	15.3	42.4	1.22*	0.61*
Z (2,−2)	−0.09 ± 1.8	1.21	3.36	2.5 ± 6.1	2.57	7.11	0.33	0.1 ± 8.3	1.51	4.19	0.1	0.4 ± 11	2.92	8.1	0.38*	0.29
Z (3,1)	−0.07 ± 0.9	0.14	0.38	0.1 ± 1.5	1.16	3.21	0.93*	0.2 ± 2.1	0.43	1.18	0.49*	0.3 ± 3.3	1.2	3.33	0.94*	0.45*
Z (3,−1)	−0.9 ± 2.9	0.12	0.33	−4 ± 5.2	0.73	2.02	0.79*	−5.3 ± 3.4	0.76	2.09	0.8*	−7.7 ± 3.8	0.73	2.04	0.79*	−0.01
Posterior																
K1 (D)	−6 ± 0.2	0.04	0.1	−6.2 ± 0.3	0.02	0.07	−0.18	−6.1 ± 0.4	0.07	0.19	0.28	−6.8 ± 0.7	0.09	0.35	0.53*	0.25
K2 (D)	−6.3 ± 0.2	0.04	0.11	−6.4 ± 0.3	0.05	0.13	0.10	−6.7 ± 0.4	0.08	0.21	0.3	−7.5 ± 0.8	0.1	0.35	0.51*	0.21
Km (D)	−6.2 ± 0.2	0.04	0.11	−6.3 ± 0.3	0.03	0.1	−0.05	−6.4 ± 0.4	0.05	0.13	0.07	−7.1 ± 0.8	0.07	0.2	0.28	0.21
Astig (D)	0.3 ± 0.1	0.05	0.14	0.3 ± 0.1	0.05	0.13	−0.03	0.6 ± 0.3	0.1	0.27	0.29	0.8 ± 0.5	0.11	0.3	0.34	0.05
BFS (mm)	6.6 ± 0.2	0.02	0.05	6.4 ± 0.3	0.02	0.05	0.06	6.4 ± 0.3	0.02	0.06	0.12	6.2 ± 0.3	0.04	0.11	0.38*	0.25
PE (μm)	11 ± 4.6	1.32	3.66	15.3 ± 6.3	1.36	3.78	0.01	39.4 ± 12.7	2.17	6.01	0.22	66.7 ± 17	2.17	6.01	0.22	0
PRC (mm)	6.4 ± 0.1	0.03	0.1	6.2 ± 0.2	0.04	0.11	0.07	5.6 ± 0.3	0.06	0.16	0.22	4.9 ± 0.4	0.08	0.21	0.34	0.12
B score	0 ± 0	0	0	0.3 ± 0.6	0.09	0.25	–[b]	2.03 ± 0.8	0.14	0.4	–[b]	4.5 ± 1.8	0.29	0.81	–[b]	0.31
RMS (total)	219 ± 15.5	1.04	2.89	229 ± 25.2	4.4	12.2	0.63*	235 ± 24	4.23	11.8	0.61*	243 ± 30	17.2	47.6	1.22*	0.61*
RMS (HOA)	6.1 ± 5.1	0.31	0.85	11.5 ± 10.7	1.94	5.37	0.8*	15.5 ± 7.4	1.5	4.16	0.69*	20.8 ± 9.7	5.05	14	1.22*	0.53*

Continued on next page

TABLE 1. Overview of Repeatability Findings in Normal and Keratoconus Eyes for Anterior and Posterior Corneal Parameters (*Continued*)

	Normal (N = 22)			Subclinical Keratoconus (N = 17)				Mild Keratoconus (N = 24)				Moderate Keratoconus (N = 26)				
	Mean ± SD	S_w	r	Mean ± SD	S_w	r	TI[a]	Mean ± SD	S_w	r	TI[a]	Mean ± SD	S_w	r	TI[a]	RI[a]
Z (2,2)	−6.4 ± 5	1.37	3.78	−9.5 ± 9.8	1.5	4.15	0.04	−10 ± 12	2.04	5.64	0.17	−13 ± 13	3.48	9.65	0.41*	0.23
Z (2,0)	217 ± 12.8	1.03	2.86	223.9 ± 18	3.77	10.4	0.56*	230 ± 21	3.75	10.4	0.56*	234 ± 27	15.3	42.4	1.17*	0.61*
Z (2,−2)	−0.3 ± 2.8	1.48	4.09	2.6 ± 6.1	2.63	7.28	0.25	0.1 ± 8.3	1.51	4.19	0.01	0.4 ± 11	2.92	8.1	0.3	0.29
Z (3,1)	−0.2 ± 2.1	0.32	0.89	0.3 ± 3	2.57	7.12	0.9*	−0.1 ± 4.3	1.01	2.81	0.5*	−0.1 ± 6.9	1.93	5.34	0.78*	0.28
Z (3,−1)	−0.5 ± 5.6	0.2	0.54	−7 ± 10.8	1.54	4.27	0.9*	−11 ± 6.4	1.2	3.33	0.79*	−16 ± 7.6	2.44	6.76	1.1*	0.31

AE = anterior elevation (maximum anterior point of elevation in 5 mm zone above the best fit sphere); ARC = anterior radius of curvature; A score = score for ARC according to ABCD grading; Astig = astigmatism; BFS = best fit sphere (8 mm); B score = score for PRC according to ABCD grading; K1 = flat keratometry; K2 = steep keratometry; Km = mean keratometry; K_{max} = maximal keratometry; PE = posterior elevation (maximum posterior elevation in 5 mm zone above the best fit sphere); PRC = posterior radius of curvature; RI = relative index: moderate compared to mild keratoconus; RMS total = root mean square (total); RMS (HOA) = higher-order aberration RMS; TI = tolerance index: comparison with normal eyes; Z (2,2) = vertical astigmatism; Z (2,0) = defocus; Z (2,−2) = oblique astigmatism; Z(3,1) = horizontal coma; Z(3,−1) = vertical coma; Zonal K_{max} (3-5 mm) = K_{max} zonal mean (3-5 mm).

[a]Statistically significant findings (TI or RI > 0.36) are indicated by an asterisk.

[b]TI for A and B score could not be calculated owing to the r value in normal eyes (r = 0).

Results for anterior and posterior corneal parameters are listed in Table 1. For subclinical keratoconus, no significant difference was found compared to normal eyes except that 5 of 7 included wavefront aberrations of both the front and back surface of the cornea (TI > 0.36 except for vertical [Z (2,2)] and oblique [Z (2,−2)] astigmatism). For the majority of parameters, there was a significant difference between moderate keratoconus compared to controls (TI > 0.36). Anterior astigmatism (RI = 0.42) and K_{max} (RI = 0.44) showed significantly worsening repeatability in more severe keratoconus, which is reflected in the substantial measurement variability in moderate keratoconus (r = 1.05 D for anterior astigmatism and r = 1.66 D for K_{max}).

The pachymetry measurements at the apex (apical corneal thickness), pupil center (central corneal thickness [CCT]), and thinnest point (thinnest corneal thickness [TCT]) showed good repeatability (TI < 0.36 for subclinical, mild, and moderate keratoconus) (Table 2). Repeatability of the densitometry readings of the anterior layer in the central 0-2 mm annulus were significantly worse for mild and moderate keratoconus (TI of 0.50 and 0.37, respectively). Other included densitometric readings showed good repeatability (Table 2; densitometry readings of posterior layer are of little interest in keratoconus and were therefore not included).

A large number of indices and combined parameters were also considered (Table 2). In subclinical and mild keratoconus, no significant differences were found for the BAD-D index compared to normal eyes (TI < 0.36). The keratoconus index and central keratoconus index also showed little worsening of repeatability in advancing disease (TI and RI < 0.36). However, the mean values of both keratoconus index and CKI did not differ between the 4 groups, which indicates that these parameters do not effectively differentiate keratoconus from normal eyes. In moderate compared to mild keratoconus, the BAD-D index (RI = 0.30) as well as the equivalent K-readings of the Holladay report (EKR65 K1 and K2 for flat and steep keratometry, respectively) (R = 0.31 and RI = 0.28, respectively) showed considerable worsening of repeatability in moderate compared to mild disease.

DISCUSSION

FOLLOW-UP OF KERATOCONUS PATIENTS ROUTINELY INvolves the evaluation of corneal measurements performed a few months apart. Progression of parameter values seen in these serial corneal measurements is the major indication for corneal cross-linking treatment.[1] Evidently, threshold values for progression should surpass the normal noise of an imaging device. Given the growing importance of corneal cross-linking, it is particularly relevant to investigate measurement accuracy in keratoconus and establish

TABLE 2. Overview of Repeatability Findings in Normal and Keratoconus Eyes for Pachymetry, Combined Parameters, and Densitometry

	Normal (N = 22)			Subclinical Keratoconus (N = 17)				Mild Keratoconus (N = 24)				Moderate Keratoconus (N = 26)				
	Mean ± SD	S_w	r	Mean ± SD	S_w	r	TI[a]	Mean ± SD	S_w	r	TI[a]	Mean ± SD	S_w	r	TI[a]	RI
Pachymetry																
ACT (μm)	548.6 ± 18.3	3.06	8.48	526.6 ± 24.7	3.06	8.47	0	511.9 ± 25.1	4.49	12.5	0.17	472 ± 40	5.27	14.6	0.24	0.07
CCT (μm)	547.9 ± 18.4	3.02	8.38	525.9 ± 24.3	3.12	8.66	0.01	514.4 ± 26	4.13	11.4	0.14	487 ± 37	4.54	12.6	0.18	0.04
TCT (μm)	544.4 ± 18.6	3.03	8.41	530.1 ± 24	3.94	10.9	0.11	498.3 ± 26.5	4.06	11.3	0.13	460 ± 38	6.31	17.5	0.32	0.19
C score	0.25 ± 0.22	0.04	0.1	0.58 ± 0.4	0.07	0.19	0.28	0.96 ± 0.5	0.09	0.24	0.37*	1.8 ± 0.8	0.13	0.36	0.55*	0.18
PPI avg	0.95 ± 0.1	0.03	0.07	1.5 ± 0.13	0.04	0.1	0.13	1.5 ± 0.2	0.07	0.2	0.45*	2.2 ± 0.5	0.13	0.35	0.68*	0.23
Combined																
BAD-D index	0.72 ± 0.43	0.13	0.36	1.98 ± 0.5	0.13	0.36	0.01	4.7 ± 1	0.25	0.7	0.30	9.5 ± 2.3	0.5	1.39	0.59*	0.30
ISV	15.5 ± 4.6	0.52	1.45	23 ± 10.8	0.93	2.57	0.25	47.7 ± 16.6	1.91	5.31	0.56*	103 ± 22.7	2.03	5.62	0.59*	0.03
IVA	0.11 ± 0.07	0.007	0.02	0.23 ± 0.2	0.02	0.05	0.41*	0.6 ± 0.2	0.04	0.1	0.67*	1.2 ± 0.3	0.03	0.08	0.59*	−0.08
KI	1.02 ± 0.02	0.005	0.01	1.06 ± 0.03	0.01	0.02	0.14	1.1 ± 0.05	0.01	0.02	0.29	1.3 ± 0.1	0.01	0.02	0.27	−0.02
CKI	1.01 ± 0.01	0.003	0.01	1 ± 0.008	0.002	0.005	−0.22	1 ± 0.02	0.01	0.01	0.21	1.1 ± 0.05	0.01	0.02	0.24	0.03
IHA	5.25 ± 3.04	1.63	4.52	9.1 ± 8.6	2.96	8.2	0.26	22.9 ± 21.6	16	44.4	0.99*	29.1 ± 23.3	18.2	50.6	1.05*	0.06
IHD	0.01 ± 0.01	0.001	0.004	0.02 ± 0.02	0.002	0.01	0.16	0.1 ± 0.03	0.005	0.01	0.55*	0.2 ± 0.05	0.005	0.01	0.55*	0.01
IS value	0.15 ± 0.64	0.06	0.17	1.2 ± 0.9	0.09	0.24	0.15	3.5 ± 1.8	0.27	0.75	0.64*	8.1 ± 3	0.24	0.66	0.59*	−0.05
EKR65 K1 (D)	42.4 ± 0.96	0.12	0.33	43 ± 1.7	0.08	0.22	−0.17	42.4 ± 2	0.32	0.88	0.42*	42.8 ± 4.3	0.65	1.79	0.73*	0.31
EKR65 K2 (D)	43.1 ± 0.9	0.11	0.32	43.7 ± 1.5	0.11	0.3	−0.03	44.5 ± 1.7	0.3	0.82	0.40*	45.7 ± 4	0.56	1.57	0.68*	0.28
Densitometry																
Dens A. 0-2 mm	27.1 ± 2.2	0.47	1.31	23.8 ± 2.9	0.93	2.59	0.30	24.8 ± 4	1.48	4.1	0.50*	25.3 ± 3.4	1.12	3.1	0.37*	−0.12
Dens A. 2-6 mm	19.8 ± 1.7	0.44	1.22	20.9 ± 2.8	0.82	2.27	0.27	21.7 ± 2.9	0.71	1.98	0.21	22.5 ± 2.6	0.86	2.38	0.29	0.08
Dens C. 0-2 mm	15.7 ± 1.4	0.2	0.57	16.4 ± 1.4	0.28	0.77	0.13	16.9 ± 1.1	0.34	0.95	0.23	16.9 ± 1.5	0.42	1.17	0.31	0.09
Dens C. 2-6 mm	14.3 ± 1.1	0.17	0.48	14.6 ± 1.3	0.19	0.52	0.04	15.1 ± 0.9	0.2	0.55	0.06	15.2 ± 1.3	0.31	0.85	0.25	0.19
Dens T. 0-2 mm	15.3 ± 1.4	0.34	0.93	16.3 ± 1.97	0.48	1.34	0.16	16.9 ± 2.2	0.63	1.75	0.27	16.8 ± 1.9	0.65	1.82	0.29	0.02
Dens T. 2-6 mm	14.1 ± 1.1	0.29	0.82	14.6 ± 1.9	0.4	1.11	0.13	15.2 ± 1.7	0.41	1.14	0.14	15.6 ± 1.6	0.55	1.51	0.27	0.12

TI = tolerance index: comparison with normal eyes; RI = relative index: moderate compared to mild keratoconus; ACT = apical corneal thickness; CCT = central corneal thickness; TCT = thinnest corneal thickness; C score = score for TCT according to ABCD grading; PPI avg = average pachymetric progression index; BAD D = Belin/Ambrosio enhanced ectasia; ISV = index of surface variance; IVA = index of vertical asymmetry; KI = keratoconus index; CKI = central keratoconus index; IHA = index of highest asymmetry; IHD = index of highest decentration; IS value = inferior-superior asymmetry; EKR65 K1 = flat keratometry of equivalent K-readings (Holladay report); EKR65 K2 = steep keratometry of equivalent K-readings (Holladay report); Dens A. 0-2 [2-6] mm = average densitometry for the anterior 120 μm in the 0-2 [2-6] mm area; Dens C. 0-2 [2-6] mm = average densitometry for central tissue in the 0-2 [2-6] mm area; Dens T. 0-2 [2-6] mm = average densitometry for total cornea in the 0-2 [2-6] mm area.

[a]Statistically significant results (TI or RI > 0.36) are indicated by an asterisk.

reliable parameters for analyzing these irregular corneas. This study provided reference repeatability values of an extensive number of relevant parameters and used the tolerance index to allow scale-independent comparison of parameters. For a criterion to be adequate at indicating progression, the repeatability limit (r) should be lower than the change needed to define progression.[2] These findings confirm that the measurement variability in keratoconus is substantially higher than in normal eyes, to such a degree that it becomes clinically relevant in the assessment of progression, especially in moderate keratoconus. This study examined the repeatability for a Scheimpflug-based device (Pentacam HR). Previous research has indicated that the variability observed in repeated measurements in keratoconus not only is observed in Scheimpflug-based imaging devices but rather is a universal issue occurring in the imaging of keratoconus eyes.[10,18]

Repeatability depends on the cohort in which measurements are made and not only on the measurement variability of the device itself. For instance, a threshold value of 1 D in K_{max} for progression of keratoconus—often applied as inclusion criterion for cross-linking trials—was based on the repeatability limit of 0.8 D reported by McAlinden and associates in a large cohort of healthy eyes examined by Pentacam.[3] These findings, along with those in literature, suggest r values of 1 to 1.5 D in mild keratoconus and 1.5 to 2 D in moderate disease.[5–9] Additionally, of the anterior curvature parameters included in this study, K_{max} had the worst RI value (RI = 0.44; r of 0.61 D and 1.66 D in mild and moderate keratoconus, respectively), closely followed by anterior astigmatism (RI = 0.42), whereas other anterior corneal curvature measurements such as anterior radius of curvature showed only mild influence of the severity of disease (RI = 0.16). Randomized trials assessing the efficacy of surgical and nonsurgical interventions in keratoconus have recently been found to exhibit poor quality of eligibility criteria, which limits the external validity of these trials.[19] A plethora of definitions of progression are used in various cross-linking trials—effectively proving the lack of consensus on this issue—but definitions often include a threshold value of 1-1.5 D increase in K_{max}.[20] Findings of poor repeatability of K_{max} in this research and previous reports add additional concern regarding the validity of results of corneal cross-linking trials. Despite the widespread use of corneal cross-linking, it remains unclear which parameters represent the best indicators of progression, which threshold values should be applied, and which parameters constitute the best outcome measures.

Applying different threshold values that depend on the stage of keratoconus or using the mean of 3-5 same-day measurements may improve decision-making.[21] Guber and associates demonstrated in their paper on measurement precision of Pentacam in keratoconus that using the average of 3 images instead of a single image reduced reproducibility limits of K_{max} to be in line with values in healthy eyes.[22] This analysis found good repeatability for the parameter "K_{max} zonal mean 3-5 mm," which represents the mean anterior dioptric value of an area of 3 up to 5 mm surrounding the steepest point. This parameter could be an alternative to K_{max} when analyzing serial measurements, but its use is currently impractical, as it needs to be manually selected on the Power Distribution screen of the Pentacam. Also, further research is required to investigate whether this parameter adequately reflects disease severity, whether it is consistent over time, and whether an area of 3, 4, or 5 mm is preferred. Using larger areas may average out changes to the cone owing to secondary flattening in the adjacent regions.

Similar to the zonal analysis surrounding K_{max}, the ARC assesses the anterior cornea by calculating the curvature radius over a 3-mm zone centered around the thinnest point as part of the "ABCD" grading system (ie, "ABCD-A").[13] These data indicate significantly worse repeatability of ARC in moderate keratoconus compared to normal eyes (TI = 0.61; eg, TI of K_{max} was 0.55). However, ARC showed markedly less influence of the severity of the cone (R = 0.16; compared to RI = 0.44 in K_{max}). This finding supports the use of a single keratoconus reference population as available on the ABCD progression display, in which reference data of a moderate-to-advanced keratoconus population is used for comparing measurements of an individual keratoconus patient.[12] Elevation-based parameters, such as anterior best-fit sphere (BFS) and anterior elevation (AE), offer a different way of analyzing the ectatic anterior corneal surface. Its repeatability has been investigated in a previous study, which reported r of 5.17 μm and 0.38 mm for AE and anterior BFS, respectively, in their cohort of 82 eyes of 57 keratoconus patients (no subgroup analysis).[6] These values are substantially higher than findings in this study (2.47 μm and 0.05 mm for AE and BFS in this moderate keratoconus group, respectively). It likely reflects differences in study population and protocol (such as their inclusion of 5 measurements per eye and the use of data from both eyes). The TI could not be compared, as the study did not include a control group.

Similar to ARC, posterior radius of curvature (PRC) is calculated based on the curvature of the 3-mm zone centered on the thinnest point of the cornea. This parameter showed good repeatability in current cohort, as did the single-point measurement posterior elevation (PE) (TI of 0.34 and 0.22 in moderate keratoconus for PRC and PE, respectively). Posterior curvature measurements (flat, steep, and mean keratometry) also showed excellent repeatability for both mild and moderate keratoconus. Use of these parameters is troubled by the low power minus dioptric value and the dependence on the index of refraction. Following cross-linking, changes in corneal hydration will likely influence the refractive

index of the cornea.[23] Posterior corneal parameters less dependent of refractive index, such as PRC or PE, are thus preferable to assess progression and the effect of cross-linking. Changes to the posterior corneal surface are typically not included in the definition of keratoconus progression for cross-linking, even though research has indicated that in progressive cases, changes to the posterior surface appear earlier than to the anterior surface.[24] Additionally, the Global Consensus stressed the importance of the posterior cornea in both diagnosis and follow-up of keratoconus.[1] Furthermore, findings in this study demonstrate a tendency of better repeatability for posterior corneal parameters compared to anterior parameters (as shown by lower TI values).

Corneal thickness measurements are of particular interest in both follow-up and eligibility assessment for surgical interventions such as corneal cross-linking and intracorneal ring segments. The 3 single-point parameters (ACT, CCT, and TCT) were consistent in this study, even in moderate keratoconus. These findings conform with previous research, indicating good repeatability of these single-point pachymetry parameters.[5,8] However, corneal thickness measurements are known to vary throughout the day.[25] A recent study examining the diurnal variation of Pentacam measurements taken 3 times a day (9 AM-5 PM) in keratoconus patients showed significant diurnal variation for TCT and CCT.[26] Repeatability (assessment of measurements taken within a very short time frame) is therefore likely a poor measure of the overall precision of this parameter. For ARC, PRC, and TCT, repeatability of subclinical keratoconus closely resembled that of the normal population. This finding conforms with the current ABCD progression display, in which 80% and 95% confidence intervals are displayed for both a normal population and a keratoconic population and the "gates" for the normal reference population are recommended for subclinical/mild disease.[12]

Previous research has indicated that the single-point pachymetry parameters have limited value in distinguishing several stages of disease and their annual change rates do not differ significantly between progressing and stable eyes.[17,22] The pachymetry progression index (PPI) reportedly has increased accuracy in distinguishing keratoconus and normal corneas compared to single-point thickness values.[27] The PPI_{Avg} shows worse repeatability than the single-point parameters, which conforms with prior research of Kosekahya and associates, who reported S_w of 0.11 for PPI_{Avg} in their cohort of 100 eyes of 100 keratoconus patients.[7] Further research is required to elucidate whether PPI is less influenced by diurnal variation compared to single-point parameters.

A number of combined topometric indices are also provided by the Pentacam software to aid in assessment of ectatic disease. Both the index of surface variance and the inferior/superior value display good repeatability in subclinical keratoconus, but markedly worse in mild-to-moderate keratoconus (TI > 0.36). These findings agree with previous research.[8] Higher-order aberrations, vertical coma (Z (3,−1)) in particular, have been studied in terms of their diagnostic value in distinguishing normal from keratoconic corneas and their ability to grade keratoconus.[28] For both the anterior and posterior cornea, these aberrations show poor repeatability in this keratoconus cohort, confirming the results of prior reports with smaller sample sizes.[9–11] Densitometry readings showed good repeatability in keratoconus with the exception of the central 0- to 2-mm radius in the anterior layer (TI of 0.50 and 0.37 in mild and moderate keratoconus, respectively), which is similar to prior research by Pahuja and associates.[29]

The BAD-D index—developed as a preoperative screening tool in refractive surgery candidates—showed good repeatability in subclinical (TI = 0.01) and mild (TI = 0.30) keratoconus, which reflects its primary use in analyzing eyes with suspect or early disease. Repeatability did worsen in more severe disease, resulting in r of 1.39 for moderate disease (TI of 0.59 vs 0.30 in moderate vs mild keratoconus). Kosekahya and associates found similar repeatability of the BAD-D index to a moderate keratoconus group in their study of 100 keratoconus eyes (no subgroup analysis).[7]

This study has some limitations. No eyes with very steep corneas (K_{max} >70 D) were included in this cohort ("severe" keratoconus). Measurement variability is expected to be even more pronounced in this group. Secondly, keratoconus eyes were not assessed following cross-linking. Pahuja and associates noticed significantly worse repeatability of densitometry 6 months following cross-linking.[29] How corneal cross-linking influences repeatability of other corneal parameters has not been studied extensively. Increased light scatter in the anterior cornea following cross-linking may affect data acquisition, especially of the posterior cornea. This study reports on the repeatability of corneal parameters on the Pentacam. Progression is, however, typically determined over time, for which reproducibility may be more clinically relevant. Future studies examining reproducibility, in which serial measurements are taken under changing conditions (such as observer, different hours in a day), are necessary to further quantify the measurement noise of corneal imaging systems such as the Pentacam. Additionally, no pediatric patients were included in this study (mean age 34 ± 9.4 years). Repeatability in the pediatric population may be worse owing to difficulties in obtaining good-quality measurements and maintaining consistent focus. Studies investigating repeatability in the pediatric population would be of great interest to further examine this potential issue.

Ophthalmologists using the Pentacam device for monitoring keratoconus patients should be aware of the instrument's measurement variability in keratoconus, as repeatability coefficients in healthy eyes cannot be

extrapolated to keratoconic eyes. Zonal measurements such as zonal means of a 3- to 5-mm area surrounding K_{max} and PRC show improved repeatability compared to single-point measurements and are promising candidates for progression analysis. K_{max} and anterior astigmatism are particularly susceptible to increasing measurement variability in more advanced disease. As there is no consensus on 1 single parameter to assess progression, it is prudent for clinicians to assess a combination of parameters to offset the test-retest variability.

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