SCIENTIFIC REPORT

Intraobserver and interobserver reproducibility in the evaluation of ultrasonic pachymetry measurements of central corneal thickness

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Purpose: To assess reproducibility of central corneal thickness (CCT) measurement by means of ultrasonic pachymetry.
Methods: Fifty one volunteers underwent three sessions of CCT measurements, each consisting of three CCT measurements, performed by each of three different observers. Intra- and interobserver reproducibility was calculated by means of intraclass correlation coefficient (ICC). The expected range of variability between two independent evaluations was calculated using scatter plots of each test-retest difference against their mean. The standard deviation of the mean differences in the test-retest scores was used to describe the differences in the score spread.
Results: The ICC ranges of the intra- and interobserver evaluations were 0.95–0.97 and 0.89–0.95 respectively; the expected variability was $\leqslant \pm 1\%$ and $\leqslant \pm$ 2% respectively (95% confidence interval).
Conclusions: The measurement of CCT by means of ultrasonic pachymetry is highly reproducible.

The measurement of central corneal thickness (CCT) is an important step in ophthalmic evaluations preceding kerato-refractive surgery.[1] It is also an increasingly important procedure in the evaluation of patients with ocular hypertension (OHT) or glaucoma.[2 3–20]

CCT can be clinically assessed by means of optical or ultrasonic pachymetry,[2] and optical coherence tomography.[21] Only a few studies have attempted to evaluate the variability of ultrasonic pachymetry: their results show a good degree of reproducibility, although most of them involved small sample sizes or were designed to compare ultrasonic pachymetry with other methods of measuring CCT.[22–29]

The aim of this study is to evaluate the variability of ultrasonic pachymeter in the clinical setting and to provide a quantitative estimate of expected CCT measurements repeated by the same or different operators.

MATERIALS AND METHODS

One eye was randomly chosen for each of 51 volunteers aged 49–82 years (31 healthy individuals, 16 patients with OHT, and four patients with primary open angle glaucoma).

Individuals with previous corneal surgery, previous or current corneal disease, and contact lens wear were excluded from the study.

Ultrasonic pachymetry was performed with an undilated pupil using an ''Altair'' Ultrasonic Pachymeter (Optikon 2000, Rome, Italy) whose probe tip is approximately 1 mm in diameter.

The pachymeter was calibrated at the beginning of each session. After the instillation of a topical anaesthetic (oxibuprocain 0.4%), the probe was placed perpendicularly on the central cornea. This was confirmed by an audible beep produced by the instrument.

Three well trained operators (EA, MG, GM) independently measured the CCT of each eye in a random sequence within 3–4 minutes of each other in order to rule out the influence of possible diurnal variations in CCT.[30–33] In order to reduce the possibility of ocular surface drying,[27] one drop of artificial tear (Dacriosol, Alcon, Fort Worth, TX, USA) was instilled 30 seconds before each measurement. Each measurement was recorded by an assistant. The observers were masked to all CCT measurement.

Intraobserver reproducibility was calculated for each of the three examiners on the basis of three consecutive measurements.

Interobserver reproducibility was based on the analysis of the three independent series of measurements made by the three examiners (nine examinations).

Reproducibility was evaluated by means of the intraclass correlation coefficient (ICC).[34–36]

The ICC was calculated for each test-retest evaluation (E1-E2, G2-G3, etc, for the intraobserver assessment; E1-M2, M3-G1, etc, for the interobserver assessment), after which the mean ICCs were calculated with their ranges.

The expected range of variability between two CCT evaluations was calculated using the paired score differences of each test minus the retest. A scatter plot was then constructed by plotting each test-retest difference against its mean. The mean value and standard deviation (SD) of the test-retest score differences were then calculated, and the SD used to describe the spread of score differences. The 95% confidence intervals of the mean difference are thus the boundaries of the expected range of variability.[37] Because the mean difference between the two repeated measurements of our 51 cases tended to be greater than zero, its value has been added to the standard calculation of 95% confidence intervals (which are also reported as per cent values around the mean measurement).

Statistical comparisons among groups were performed using Friedman's non-parametric test; the statistical comparisons between two groups were made using Mann-Whitney's non-parametric test.

Linear regression analysis was performed to evaluate whether there was a linear association between test-retest score difference and CCT value.

A variation of $\geqslant$15 μm between two repeated measurements has been considered as a clinically relevant outcome (as it can induce an error in intraocular pressure (IOP)

Abbreviations: CCT, central corneal thickness; ICC, intraclass correlation coefficient; IOP, intraocular pressure; OHT, ocular hypertension

Table 1 Descriptive statistic of the CCT* measurements (μm) performed by the three observers

	Mean	SD
M1	571.49	35.17
M2	567.96	34.18
M3	568.84	36.81
M mean	569.43	35.39
E1	570.47	34.19
E2	568.94	35.30
E3	569.20	34.01
E mean	569.54	34.50
G1	567.02	35.73
G2	564.45	34.90
G3	564.12	35.61
G mean	565.20	35.41

*Central corneal thickness.

assessment of about 1 mmHg according to the conversion factor of Ehlers and colleagues of 0.7 mmHg/10 μm^4), and the frequency with which these substantial changes occurred has been calculated.

RESULTS

The descriptive statistics for each observer are summarised in table 1. The mean CCT measurements of the three observers were statistically different ($p = 0.002$).

Intraclass correlation coefficient

The mean ICC for intraobserver reproducibility was 0.966 (SD 0.009) and ranged from 0.949 to 0.981. The mean ICC for interobserver reproducibility was 0.935 (SD 0.016) and ranged from 0.890 to 0.957. The ICCs of the intra- and interobserver analyses were significantly different ($p < 0.0001$). The ICCs obtained by comparing observer M *v* E were not significantly different from those obtained by comparing observers M or E *v* G ($p = 0.4$).

Scatter plots

The expected intra- and interobserver measurements are shown in table 2. The mean expected intraobserver measurement was within $\pm 0.75\%$ and the largest observed value was $< \pm 1.10\%$; the mean expected interobserver measurement was within $\pm 1.20\%$ and the largest observed value was $< \pm 2\%$.

The mean expected measurements in the intraobserver and interobserver analyses were significantly different ($p = 0.002$). The mean expected measurements obtained by challenging observer M *v* E was significantly smaller than that obtained by challenging observers M or E *v* G ($p < 0.0001$). Test-retest score difference did not regress on CCT value (r resulted less than 0.2 and $p > 0.1$ in all analyses).

Clinically relevant changes

A variation of ⩾15 μm between two repeated measurements occurred in 52 out of 459 (11.3%) test-retest intraobserver

Table 2 Scatter plots and mean expected range of variability from each test-retest evaluation

Test-retest	Mean*	Difference*	SD*	95% CL*†	±95% CL (%)†
Intraobserver analysis					
M1–M2	569.7	3.5	9.1	563.6–575.8	1.07
M1–M3	570.1	2.6	11.2	564.3–575.9	1.02
M2–M3	568.6	0.9	10.7	564.6–572.6	0.70
E1–E2	569.7	1.5	7.4	566.0–573.3	0.64
E1–E3	569.8	1.2	7.8	566.3–573.3	0.61
E2–E3	569.1	0.2	8.0	566.5–571.5	0.44
G1–G2	565.7	2.5	8.0	560.9–570.5	0.85
G1–G3	565.5	2.9	10.8	559.6–571.5	1.05
G2–G3	564.2	0.3	6.8	562.0–566.5	0.40
Mean	568.0	1.7	8.9	563.7–572.3	0.75
Interobserver analysis					
M1–E1	570.9	1.0	11.0	566.8–575.1	0.72
M1–G1	569.2	4.4	15.9	560.2–578.2	1.57
E1–G1	568.7	3.4	11.2	562.1–575.3	1.16
M2–E2	568.4	0.9	11.5	564.2–572.6	0.74
M2–G2	566.2	3.5	10.7	559.6–572.7	1.15
E2–G2	566.6	4.4	11.0	559.0–574.3	1.34
M3–E3	569.0	0.3	12.8	565.0–572.9	0.69
M3–G3	566.4	4.7	12.9	558.1–574.8	1.47
E3–G3	566.6	5.0	9.0	559.0–574.2	1.34
M1–E2	570.2	2.5	12.0	564.2–576.1	1.04
M1–E3	570.3	2.2	11.7	564.7–575.9	0.98
M1–G2	567.9	7.0	12.5	557.4–578.5	1.86
M1–G3	567.8	7.3	12.5	556.9–578.6	1.92
M2–E1	569.2	2.5	10.9	563.6–574.8	0.98
M2–E3	568.5	1.2	11.1	564.1–572.9	0.77
M2–G1	567.4	0.9	14.3	562.5–572.4	0.88
M2–G3	566.0	3.8	11.4	558.9–573.1	1.25
M3–E1	569.6	1.6	13.8	564.1–575.1	0.97
M3–E2	568.8	0.1	13.5	564.9–572.7	0.69
M3–G1	567.9	1.8	17.0	561.3–574.5	1.17
M3–G2	566.6	4.3	13.1	558.5–574.7	1.43
E1–G2	567.4	6.0	9.6	558.7–576.1	1.54
E1–G3	567.2	6.3	9.5	558.2–576.3	1.59
E2–G1	567.9	1.9	12.5	562.5–573.4	0.96
E2–G3	566.5	4.8	10.8	558.6–574.3	1.39
E3–G1	568.1	2.1	12.8	562.3–573.8	1.02
E3–G2	566.8	4.7	10.0	559.2–574.3	1.33
Mean	568.0	3.3	12.0	561.3–574.7	1.18

*Values expressed in μm
†95% confidence limits.

evaluations, and in 304 out of 1377 (22%) test-retest inter-observer evaluations.

DISCUSSION

There is considerable amount of published data suggesting a relationship between IOP and the risk of glaucoma,[19 38–41] and CCT and the risk of glaucoma.[2 20]

We investigated the intra- and interobserver reproducibility of CCT measurements made using an ultrasonic pachymeter.

The descriptive statistics show that, although similar, the mean measurements made by the three observers were statistically different. However, this bias was extremely small as it could be estimated in only about 0.7% of the mean CCTs observed in our sample.

The analyses of intra- and interobserver reproducibility showed almost perfect agreement (ICC being between 0.81 and 0.99), and the mean expected variability found in the series of each single test-retest comparison was $\leqslant 1.92\%$.

Our results seem to indicate that both the intra- and inter-observer reproducibility of CCT measurements is extremely high. The fact that the instrument used in this study does not have a fixation light, and the fact that the probe diameter is only 1 mm (which may have induced some variation in its positioning on the cornea) may have contributed to variability in CCT measurements.

A further potential source of variability lies in the corneal touch technique. Our results in fact show that the CCT measurements made by different observers may be slightly different, and that the difference observed between the intra- and interobserver analyses was statistically significant.

The extent of variability between each test-retest did not depend on the absolute CCT value in any comparison, both in the intra- and interobserver evaluations.

A variation of $\geqslant \pm 15$ μm between two repeated measurements occurred in 11.3% test-retest intraobserver evaluations, and in 22% test-retest interobserver evaluations. This indicates that, despite the high reproducibility of the procedure, care should be taken in the interpretation of IOP measurement corrected on the basis of CCT measurement. In fact, it is possible to expect 10% of the CCT measurements to induce an incorrect IOP estimate of about ± 1 mmHg also when the same operator performs the CCT examinations.

Our study confirms the results of previous studies[22–29] and provides a quantitative estimate of the CCT measurements that can be expected from repeat examinations.

The variability of IOP measurements made using the Goldmann applanation tonometer may be $\geqslant 2$ mmHg in about 20–30% of subjects.[42–44] If we assume that variations in CCT affect accurate applanation tonometry readings and apply Ehlers' CCT correction factor (the largest reported so far) to more accurately determine IOP,[4] the variability in ultrasonic pachymetry CCT measurements is less than the variability inherent in Goldmann tonometry IOP evaluations. This means that routine ultrasonic pachymetry CCT measurements should not introduce additional sources of error in clinical practice.

The results of our study suggest that the relatively simple, highly reproducible and objective nature of ultrasonic pachymetry should allow any well trained operator to make highly reliable CCT measurements.

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ECHO

Gene variant in primary open angle glaucoma

Please visit the *British Journal of Ophthalmology* website [www.bjophthalmol.com] for a link to the full text of this article.

Primary open angle glaucomas (POAGs) affect around 1–2% of people and are a major cause of blindness in Western countries. Some patients with POAG have normal tension glaucoma (NTG, intraocular pressure <21 mm Hg) and it is not clear whether these patients have a different pathology. Genetic factors are important in POAG but the genetics is complex. The OPTINEURIN (OPTN) gene on the short arm of chromosome 10 (10p14) has been implicated in NTG and the M98K variant is more common in POAG patients. Now a study in France and Morocco has shown that this variant is associated with lower initial intraocular pressure in patients with POAG.

The study included 237 patients with POAG and 110 controls (healthy spouses) in France and 56 patients and 60 general population controls in Morocco. The M98K variant of the OPTN gene was found in 4.6% of cases and 4.5% of controls in France and in 10.7% of cases and 8.3% of controls in Morocco. There was no significant difference between cases and controls but the M98K variant was twice as frequent in Morocco. The variant was associated with normal or moderately increased pressure glaucoma. Initial intraocular pressure (before treatment) was lower in patients with the variant allele (mean pressure 25.9 mm Hg (M98K positive) *v* 32.3 mm Hg (M98K negative) in the French groups (highly significant), and 32.3 *v* 37.3 mm Hg in Moroccan group (not significant)). For the pooled populations mean initial intraocular pressure was highly significantly lower (28.2 *v* 33.4 mm Hg) in M98K positive patients.

The M98K variant of the OPTN gene does not increase the risk of POAG but it is associated with lower initial intraocular pressure in patients with POAG.

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