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Discrepancy in Specular Microscopy-Measured Central Corneal Thickness Between Both Eyes of a Patient

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We reported the differences of central corneal thicknesses（CCT）between both eyes . In our study, CCTs were measured using three types of specular microscopes, ultrasound pachymeter , and rotating Scheimpflug camera . We found that the CCTs measured by various specular microscopes differed between the right and left eyes, but this discrepancy has not been seen with ultrasound pachymetry or the rotating Scheimpflug camera. Although the mechanism of this discrepancy was unknown, to avoid differences in CCTs in both eyes, the manufacturers may be recommended to calibrate the specular microscopic devices with human subjects rather than the model eye and be advised applying the different conversion coefficients for each right and left eye. Still further, we need to understand the characteristic of each device and utilize the result for the evaluation of diseases.

Key words: central corneal thickness, specular microscope, ultrasound pachymeter, rotating Scheimpflug camera Pentacam, glaucoma

INTRODUCTION

Individual differences in central corneal thickness（CCT）affect the intraocular pressure（IOP）measurement using applanation and other tonometers［1-3］; the IOP readings are lower than the true IOP value with thinner corneas and vice versa. Underestimation of the IOP in patients with primary open-angle glaucoma（POAG）with thin corneas may lead to misdiagnosis of normal tension glaucoma, while overestimation of the IOP in normal subjects with thick corneas may lead to misdiagnosis of ocular hypertension［4-9］.

On one hand Herndon *et al* showed that lower CCT was significantly associated with advanced glaucoma［14］, on the other hand Shah *et al* advocated that thick CCTs may not need to be followed as glaucoma suspect eyes［9］. Therefore, to eliminate the effect of the differences in the CCTs on the IOP measurements, various equations have been proposed for normal and glaucomatous eyes and those that underwent a refractive surgery［10, 11］. Other than errors in the IOP measurement, the CCT itself predicts development or progression of POAG［12-16］; therefore, measurement of the CCT has become essential for managing glaucoma.

The clinically relevant accuracy and/or reproducibility of CCT measurements has been reported previously with various contract and non-contact devices including specular microscopes［17, 18］, the rotating Scheimpflug camera Pentacam（Oculus, Wetzlar, Germany）［19-21］, ultrasound pachymeters［17, 19, 20, 22］, the scanning slit topographer Orbscan［20,24,29,30,32,33,39］, ultrasound biomicroscopy［22,41］, and optical coherence tomography（OCT）［21,35］. Because of its non-contact methodology and even better reproducibility than contact ultrasound pachymetry［23-25］, specular microscopy

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has been used widely to measure the CCT in clinical settings and epidemiologic studies [26, 27].

In the current retrospective multicenter review of medical records, we found that the CCTs measured by various specular microscopes can differ between both eyes of a patient systematically. This discrepancy has not been seen with ultrasound pachymetry or the Pentacam.

MATERIALS AND METHODS

This study included two different populations in studies 1 and 2. The Institutional Review Board of Shimane University Hospital reviewed and approved all protocols. The studies complied with the tenets of the Declaration of Helsinki. Based on the regulations of the Japanese Guidelines for Epidemiologic Study 2008 issued by the Japanese Government, the study protocols did not require the each patient provide written informed consent.

For study 1, the CCT data from 1,358 eyes of 679 subjects (251 men, 428 women; mean age ± standard deviation [SD], 75.1 ± 8.8 years) were collected by reviewing the medical records in four institutions. The CCTs were measured in all subjects using one of three specular microscopes (EM-3000, Tomey, Nagoya, Japan; SP-3000P, Topcon, Tokyo, Japan; or NSP-9900, Konan Medical, Nishinomiya, Japan) during a preoperative examination for cataract surgery. For the data collection, the medical records of all subjects that appeared on surgical lists for cataract surgery during a 6-month period were reviewed in each institute; subjects were excluded when the CCT was not recorded or recorded in only one eye. Subjects were included when the CCTs of both eyes were recorded.

For study 2, the CCT data from 216 eyes of 108 subjects (45 men, 63 women; mean age ± SD, 67.8 ± 13.9 years) with glaucoma were collected consecutively by reviewing the medical records at Shimane University Hospital. The CCTs were measured in both eyes of all subjects using all three corneal thickness measurement devices including the specular microscope (Tomey EM-3000), ultrasound pachymeter (TomeyAL-3000), and the Pentacam to diagnoses glaucoma and/or for the preoperative evaluation. In study 1, the three specular microscopy models were compared with consideration of the patient age, the CCTs from both eyes analyzed by one-way analysis of variance (ANOVA) followed by Scheffe's post hoc test, and gender analyzed using the G-square test. In each device group, the paired t-test was used to compare the CCTs between both eyes. In study 2, the CCTs in all subjects were measured using all three devices; therefore, to compare the devices, the CCTs from both eyes were compared by repeated measurement ANOVA followed by the Bonferroni-corrected paired t-test. In each device group, the CCTs were compared between both eyes using the paired t-test. Statistical analyses were performed using StatView software, version 5.0 (SAS Institute Inc., Cary, NC) on a Macintosh personal computer (Apple Inc., Cupertino, CA). All statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

RESULTS

The demographic data collected from the subjects in study 1 are summarized in Table 1. The gender and age did not differ significantly among the three specular microscopy groups. The CCTs from the right and left eyes and the difference in the CCTs between both eyes measured by the different specular microscopes are summarized in Table 2. In the right and left eyes, the mean CCT values were significantly ($p < 0.0001$ for all comparisons) thicker in the NSP-9900 group than the other two groups and significantly thicker ($p < 0.0001$ for right eye and $p = 0.0275$ for left eye) in the EM-3000 group than the SP-3000P group. Interestingly, when both eyes of a patient were compared in each device group, the CCTs were significantly thicker in the right eye than the left eye in the EM-3000 group ($p < 0.0001$), but were thicker in the left eye than the right eye in the SP-3000P ($p = 0.0833$) and the NSP-9900 ($p = 0.0424$) groups.

Since the CCTs compared among the devices in study 1 were obtained from different subject groups, we next collected the CCT data measured by the three different devices (i.e., specular microscope, Pentacam, and ultrasound pachymeter) in the same subjects. The CCTs from the right and left eyes and the difference in the CCTs between both eyes

Table 1. Demographic data of the subjects in Study 1

	Devices			
	A Tomey EM-3000	B Topcon SP-3000P	C Konan NSP-9900	p-value
No. of subjects/eyes	309/618	200/400	170/340	
Male/Female	111/198	85/115	92/117	0.1160*
(%)	40/60	43/57	55/115	
Age (yrs)				
mean+/-SD	74.9+/-9.5	75.3+/-8.5	75.4+/-7.7	0.7953**
range	37-98	39-93	52-90	
Institutes	Shimane University Hospital (204 subjecsts) and Ichioka Clinic (105 subjects)	Masuda Eye Clinic	Ichioka Eye Clinic	

*P value is calculated by G-square test
**P value is calculated by one-way ANOVA

Table 2. Central corneal thickness in Study 1

	Devices			
CCT (μm)	A Tomey EM-3000	B Topcon SP-3000P	C Konan NSP-9900	p-value
Right eye				
mean +/- SD	530.1 +/- 36.6	511.2 +/- 32.9	557.4 +/- 38.9	< 0.0001*
range	400 - 636	420 - 588	456 - 651	
		P < 0.0001 vs. A**	P < 0.0001vs. A**	
			P < 0.0001 vs. B**	
Left eye				
mean +/- SD	521.9 +/- 35.9	513.1 +/- 31.9	560.8 +/- 40.4	< 0.0001*
range	383 - 631	433 - 606	453 - 671	
		P = 0.0275 vs. A**	P < 0.0001vs. A**	
			P < 0.0001 vs. B**	
Right eye - Left eye				
mean+/-SD	+8.3 +/- 17.0	-1.9 +/- 15.1	-3.5 +/- 22.1	
range	-97 - +92	-41 - +60	-78 - +64	
R vs. L	P < 0.0001***	P = 0.0833***	P = 0.0424***	

*, **P values are calculated by one-way ANOVA (*) followed by Scheffe'sposthoc test (**) among 3 devices in each of right and left eyes
***P values are calculated by paried t-test between right and left eyes in each devices
CCT, central corneal thickness

in study 2 are summarized in Table 3. In the right and left eyes, the mean CCT values were significantly ($p < 0.0001$ for all comparison groups) thicker in the Pentacam group than the EM-3000 and ultrasound pachymetry AL-3000 groups. Comparison of both eyes in each device group showed significantly ($p < 0.0001$) thicker CCTs in the right than left eyes in the EM-3000 groups, while differences between the right and left eyes were not seen in the AL-3000 ($p = 0.7715$) or the Pentacam ($p = 0.9739$) groups (Table 3).

DISCUSSION

The CCTs measured may differ between devices as reported previously when the specular microscopy was compared with ultrasound pachymetry [17, 22-25, 28]. Pentacam [20, 29], and Orbscan [24, 29, 30]; when the Pentacam was compared with ultrasound pachymetry [19, 31], OCT [21], partial coherence interferometry [32], and Orbscan [20, 29, 33]; and when ultrasound pachymetry was compared with OCT [34, 35] and Orbscan [20]. Thus, the current results of different CCTs among devices in studies 1 and 2 agreed with the result of the previous reports.

Other than confirming different CCT values among the devices, we found a difference in the CCTs between both eyes when the CCT was measured by three specular microscopy models (Table 2). With Topcon SP-3000P device, the difference did not reach statistically significant ($p = 0.0833$). Using Topcon SP-2000P, the Tajimi study and its related studies reported 2 to 3 μm thicker CCTs in left eyes than right eyes [26, 27]. By our own calculation using t-test, the both eyes differences in these studies reached statistically significant ($p = 0.0001$-0.0190). Thus, the Topcon device also can differ in the CCTs between both eyes. The CCTs were identical between both eyes with the Pentacam and ultrasound pachymetry in the current (Table 3) and previous studies [36, 37]. Thus, the difference in the CCTs between both eyes was seen systemically with specular microscopy devices.

The Pentacam system measures the CCT on the series of Scheimpflug images that obtained by a

Table 3. Central corneal thickness in Study 2

	Devices			
CCT (μm)	A Specular microscopy Tomey EM-3000	B Ultrasound pachymetry Tomey AL-3000	C Scheimpflug camera Oculus Pentacam	p-value
Right eye				
mean +/- SD	525.4 +/- 41.4	526.0 +/- 40.3	540.8 +/- 40.2	< 0.0001*
range	400 - 670	409 - 692	435 - 681 P < 0.0001 vs. A** P < 0.0001 vs. B**	
Left eye				
mean +/- SD	517.6 +/- 38.9	526.4 +/- 39.1	540.9 +/- 39.1	< 0.0001*
range	383 - 634	412 - 657	439 - 653 P < 0.0001 vs. A** P < 0.0001 vs. B**	
Right eye - Left eye				
mean+/-SD	+7.8 +/- 19.4	-0.4 +/- 14.5	-0.1 +/- 17.6	
range	-50 - +55	-48 - +35	-58 - +43	
R vs. L	P < 0.0001***	P = 0.7715***	P = 0.9739***	

*, **P values are calculated by repeated measrement ANOVA (*) followed by Bonferroni-corrected paired t-test (**) among 3 devices in each of right and left eyes

***P values are calculated by paried t-test between right and left eyes in each devices

CCT, central corneal thickness

rotation of camera on the axis though the corneal apex [19, 38]. Ultrasound pachymetry measures the CCT at the examiner-determined center of the cornea that perpendicular to the corneal surface [19, 38]. Slit lamp-based detection of corneal topography is the common rationale of the CCT measurement by specular microscopy [17, 23]. With this type of device, reflection peaks from the inner and outer corneal surfaces were detected by the detector that positioned on the opposite side of the light source. From the obtained peak width, the CCT then is calculated by the trigonometric function with a conversion coefficient. This rationale allows the proper CCT estimation when the cornea is evenly thick around the corneal center. Accordingly, factor of the laterality lies only in the rationale of specular microscopy might associate with the discrepancy.

We found that the thicker/thinner side of CCTs changes in each model of specular microscopy. Previous studies have shown that both the peripheral (4.5 mm from the center) and mid-peripheral (2.75 mm from the center) corneal thicknesses were thicker nasally than temporally using ultrasound pachymetry [39]; the pericentral cornea was thicker in the nasal quadrant compared with the temporal quadrant with topographic analysis using OCT [40]. Thus, it is reasonable to suggest that if the light passes through the nasal cornea, a thicker CCT value is obtained than when the light passes through the temporal cornea. However, based on the information provided by the manufacturers, the light source is placed on the right side of the subjects in all three specular microscopy devices tested. Accordingly, laterality of the light path does not explain the mechanism of thicker/thinner side of CCTs changes in each model of specular microscopy, and therefore, the mechanism still needs to be clarified in the future.

The CCT data analyzed in the current study were collected retrospectively from the subjects in study 1 who underwent preoperative examinations for cataract surgery or subjects in study 2 who underwent glaucoma diagnostic examinations at a university hospital. Thus, the methods or examiners of the CCT measurements were not predetermined among subjects or centers, and the background, including the ocular and systemic history, refractive errors, or IOP, also were not homogenous among the subjects. However, in study 1, the population scheduled for cataract surgery was expected to not different greatly among centers given the similar age and gender distributions among the devices (Table 1). In study 2, the differences in the individual backgrounds were irrelevant since the same subjects with glaucoma underwent repeated measurements of the CCTs with different devices. Consecutive collection of a large amount of data should eliminate individual variations in CCTs between both eyes. Thus, we believe that the current comparisons of the CCTs between the device groups and between both eyes were scientifically reasonable.

Collectively, the CCTs measured by specular microscopy differed between the right and left eyes. The discrepancy, 8.3 μm at most, may not be critical for the management of each individual patients, however, may affect the clinical studies that set the CCTs as outcome measures. Generally, the device is calibrated using a model eye in which the corneal thickness is homogenous. To avoid differences in CCTs in both eyes, the manufacturers are recommended to calibrate the specular microscopic devices with human subjects rather than the model eye and are advised applying the different conversion coefficients for each right and left eye. Still further, we need to understand the characteristic of each device and utilize the result of CCTs for the evaluation of diseases clinically.

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