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Central and Peripheral Autorefractive Repeatability in Normal Eyes

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Abstract

Purpose—To determine the between-visit repeatability of peripheral autorefractive measurements using the Grand Seiko WAM-5500 in normal eyes.

Methods—Cycloplegic autorefractive of the right eye was measured on 25 myopic young adults using a modified Grand Seiko autorefractor. Measurements were made centrally (along the line of sight) and $\pm 20^\circ$, $\pm 30^\circ$, and $\pm 40^\circ$ from the line of sight in the horizontal meridian at two visits separated by 1 to 15 days. Five autorefractive measurements at each location were converted to vector space and averaged. Relative peripheral refraction (RPR) was calculated as the difference between the peripheral and central spherical equivalent (SE). Between-visit repeatability was evaluated by plotting the difference versus the mean of the measurements at the two visits (bias) and by calculating the 95% limits of agreement (LoA).

Results—The mean ($\pm$ SD) age and SE refractive error centrally (at visit 1) were 24.0 ± 1.3 years and -3.45 ± 1.42 D, respectively. There was no significant between-visit bias for any refractive component evaluated (M, J0, J45, and RPR) at any location measured (all $p > 0.05$). The 95% LoA of defocus (M) was ± 0.21 D centrally and increased with increasing eccentricity to ± 0.73 D and ± 0.88 D at 40° nasally and temporally on the retina, respectively. The 95% LoA of RPR increased with increasing eccentricity to ± 0.67 D and ± 0.82 D at 40° nasally and temporally on the retina, respectively.

Conclusions—In normal eyes, the repeatability of cycloplegic autorefractive was best centrally and decreased as eccentricity increased; however, repeatability in the far periphery was still better than previously reported between-visit repeatability for foveal cycloplegic subjective refraction. With clear knowledge of the repeatability of on- and off-axis cycloplegic autorefractive with the Grand Seiko, peripheral measurements can be properly interpreted in longitudinal studies.

Keywords

between-visit repeatability; myopia; relative peripheral refraction; peripheral defocus; cycloplegic autorefractive

Open-field autorefractive is frequently used in studies to objectively measure changes in central (on-axis) refractive error over time. While central refractive error is commonly

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measured in studies of myopia, peripheral refractive error is increasingly being measured as well. The suggestion of a potential role of peripheral refractive error on the development of myopia dates back to the 1970's.¹ With recent work in animal models providing convincing evidence that peripheral defocus influences eye growth and that local regions of the retina can respond to local defocus signals,^{2, 3} open-field autorefractors are commonly being used to measure peripheral refractive error of the eye as a surrogate for eye shape and to determine peripheral defocus.^{4, 5} Several studies have evaluated longitudinal changes in peripheral refractive error and the influence of optical treatments on peripheral defocus.⁶⁻⁹ As new optical treatments are investigated in myopia control studies, it will be important to know the off-axis repeatability of open-field autorefraction in order to determine whether peripheral defocus caused by optical interventions results in a change in peripheral refractive error over time.

Grand Seiko autorefractors (Grand Seiko Co., Hiroshima, Japan), also marketed under the name Shin-Nippon, are frequently used in longitudinal studies because of their well-documented accuracy and repeatability when measuring central refractive error and the ability to use real targets of the investigator's choice due to its open-field design.¹⁰⁻¹⁴ Despite the instrument increasingly being used to measure off-axis refractive error over time, studies of between-visit repeatability of peripheral measurements are scarce with the only report of which we are aware being in patients who have undergone orthokeratology treatment.¹⁵ Myopic orthokeratology reshapes the cornea leading to significant central flattening and mid-peripheral corneal steepening.¹⁶ These corneal changes may increase sensitivity to misalignment of the autorefractor when making peripheral measurements because the measurement beam passes through the markedly steeper mid-peripheral corneal zone when making these measurements. Knowing the repeatability of off-axis measurements in the presence of a normal corneal shape will allow for proper interpretation of longitudinal peripheral refraction results, which could aid in understanding whether optical corrections other than orthokeratology have a meaningful influence on eye shape.

The purpose of this study was to determine the between-visit repeatability of the Grand Seiko WAM-5500 open-field autorefractor in the horizontal meridian of normal eyes. The between-visit repeatability of both peripheral refraction (the actual refractive error measured at each location) and relative peripheral refraction (RPR) were determined.

METHODS

Subjects

Twenty-five non-presbyopic adults (22 to 27 years old) were enrolled. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the University of Houston Committee for the Protection of Human Subjects. Subjects reviewed and signed an informed consent document before enrollment in the study. All subjects had spherical equivalent correction at the corneal plane of -0.50 D or more myopia and best-corrected Snellen visual acuity of better than 20/25. All subjects were free of any ocular disease, had no history of ocular trauma or surgery, and had no history of any systemic disease known to cause variability in refractive error. Rigid gas permeable contact lens wearers were

excluded. All subjects were instructed to wear glasses on the days of their study appointments.

Autorefracton Measurements

Cycloplegic measurements of the right eye were made using a Grand Seiko WAM-5500 autorefractor that was modified to allow measurements out to $\pm 40^\circ$ from the line of sight. An attachment added to the top of the autorefractor held a red laser diode that could be placed in wells so that a small, red laser spot could be presented on a blank wall centrally (along the line of sight) and out to 40° nasally and temporally from the line of sight in 10° increments. The autorefractor was positioned such that the distance from the entrance pupil to the wall when looking in primary gaze was 1.5 meters. Subjects were instructed to look at the center of the small laser spot target. Measurements began 30 minutes after instilling the first of two drops of 1% tropicamide that were separated by 5 minutes. Each subject wore a patch over the left eye to ensure accurate fixation by the tested eye.

Measurements were made centrally and at $\pm 20^\circ$, $\pm 30^\circ$, and $\pm 40^\circ$ from the line of sight on the retina in the horizontal ocular meridian. The autorefractor measurement axis was centered horizontally within the entrance pupil for all measurements to maximize peripheral refraction accuracy.¹⁷ Subjects were given clear instructions to point their nose at the peripheral target while keeping their eye in primary gaze. The examiner visually inspected the subject's alignment prior to each measurement to make sure their head was properly rotated for each new viewing angle and that their nose was pointing to the target. If the subject was not rotating their head properly, the examiner viewed the subject's position from above and re-positioned their head so that their nose pointed at the target. A wider, custom chin rest was used to allow for lateral head movement for proper positioning to view the peripheral targets. Approximately 10 measurements were made at each location to ensure that a total of 5 measurements at each location were available that were within 1.00 D of the mode of the sphere and the cylinder readings, a strategy consistent with the approach utilized by other studies to objectively eliminate spurious readings caused by circumstances such as blinks or brief fixation losses.^{15, 18, 19} Subjects returned for a second visit 1 to 15 days after their first visit, and the cycloplegic measurements were repeated.

Data Analysis

Autorefracton values at each retinal location were transposed into vector components (M, J_0 , and J_{45}) using previously described methods and were averaged.²⁰ RPR at each peripheral location was calculated by subtracting the mean central defocus (M) from the mean peripheral defocus.

Statistical analyses were performed using STATA 13.1 (Stata Corp., College Station, TX). Between-visit repeatability was assessed using methods described by Bland and Altman.²¹ The difference between each pair of measurements at the two visits was calculated for each refractive value (M, J_0 , J_{45} , and RPR) at each retinal location. The mean of the differences between visits describes the bias. Each mean difference was compared to zero using a t-test with the exception of when differences were found not to be normally distributed by a Shapiro-Wilk test, in which case a non-parametric sign test was used instead. The

relationship between the differences and means for each refractive value at each location was also evaluated using either a Pearson correlation or a Spearman correlation (when non-parametric testing was appropriate). The 95% limits of agreement (LoA) were calculated as the mean difference $\pm 1.96 \times$ standard deviation of the differences.

RESULTS

The mean ($\pm$ SD) age and central cycloplegic spherical equivalent autorefraction (at visit 1) of the subjects were 24.0 ± 1.3 years and -3.45 ± 1.42 D, respectively. Of the 25 subjects, 18 (72%) were female. Central and peripheral autorefraction results, bias, and repeatability ($\pm 1.96 \times$ SD of the differences) are shown in Table 1. RPR results, bias, and repeatability are shown in Table 2. The bias (difference between visits) was not significantly different than zero for M, J₀, J₄₅, or RPR at any location measured (all $p > 0.08$). A difference versus mean plot of the central spherical-equivalent defocus(M) between-visits is shown in Figure 1, and difference versus mean plots for peripheral defocus (M) between visits are shown in Figure 2 at each peripheral location measured. For all refractive values (M, J₀, J₄₅, and RPR), repeatability was best centrally and became less repeatable as eccentricity increased.

As expected, relative peripheral hyperopic defocus was found in these myopic eyes, and relative peripheral hyperopia was greatest at the most eccentric measurement location (Table 2). At more peripheral locations along the horizontal meridian of the eye, J₀ astigmatism also increased as measurements were made through more peripheral portions of the cornea and crystalline lens (Table 1). Small increases in J₄₅ (oblique) astigmatism were observed as eccentricity increased, though changes in oblique astigmatism were relatively small (just over 0.25 D at 40°).

DISCUSSION

Repeatable measurements of central refractive error have long been important in longitudinal studies of refractive error development. With both animal^{2, 3} and human⁹ studies suggesting a role for peripheral defocus in myopia progression, an increasing number of studies are measuring peripheral refraction. Because local retinal regions have been shown to respond to local defocus signals in animal models,^{3, 22} determining whether changes in peripheral refractive error occur over time in studies of optical interventions is important.²³ Previous studies have shown the Grand Seiko to have good on-axis, between visit repeatability,^{12, 13, 24} and the Grand Seiko has been used as the standard against which to compare other methods of measuring peripheral refractive error (such as aberrometry-based methods).^{25, 26} That being said, to our knowledge, the between-visit repeatability of peripheral refraction measurements using the Grand Seiko autorefractor has not been reported in normal eyes that have not undergone any type of refractive surgery or corneal reshaping.

The Grand Seiko showed excellent central, between-visit repeatability for spherical-equivalent defocus, J₀, and J₄₅, which became progressively less repeatable with increasing eccentricity. The central 95% LoA for cycloplegic spherical-equivalent defocus in our study of normal eyes (± 0.21 D) was better than previously reported in several studies without

cycloplegia (range: ± 0.43 to ± 0.86 D)^{11, 12, 14, 24} and with cycloplegia in eyes after LASIK surgery (± 0.47 D).¹³ An advantage of our study is that measurements were made under cycloplegia and eyes had not undergone refractive surgery. These factors likely account for the better central repeatability found in our study because the typical prolate shape of the cornea was unaltered and cycloplegia eliminated the potential for variable accommodation.

The between-visit 95% LoA for spherical-equivalent defocus in the far periphery (± 0.73 D nasally and ± 0.88 D temporally) were still good when compared to the reported between-visit 95% LoA of cycloplegic subjective refraction (± 0.94 D).²⁷ The repeatability of J_0 astigmatism in the periphery was similar to that of defocus. The repeatability of J_{45} astigmatism in the horizontal meridian of the eye was better than the repeatability of M and J_0 in the periphery with a smaller decrease in repeatability at higher eccentricities. The better repeatability for J_{45} astigmatism is likely because measurements were made in the horizontal meridian of the eye where peripheral increases in astigmatic error are expected to be due to differences in power along the horizontal and vertical meridian. Had peripheral measurements been made along an oblique meridian, we might expect the repeatability of J_{45} to decrease more similarly to the change seen in J_0 astigmatism along the horizontal meridian.

One contributing factor to the decrease in repeatability of defocus, J_0 , and J_{45} measurements further in the periphery may be the reported influence of lateral pupil misalignment when autorefractor measurements are made at higher eccentricities. Fedtke et al. reported that even a 0.27 mm lateral misalignment of the pupil center with the instrument axis when measuring 30° in the periphery of a myopic eye could cause a 0.25 D change in peripheral defocus.¹⁷ This might be due to increased higher-order aberrations at more eccentric locations of the visual field when light travels through the peripheral cornea and crystalline lens.²⁸ Despite taking great care to ensure that the Grand Seiko measurement beam was centered in the pupil before taking measurements, subtle misalignment errors not detected by the examiner may have contributed to the increased variability observed in the far periphery.

There was a slight asymmetry in the repeatability of defocus measurements between the nasal and temporal retinal locations. One might hypothesize that because peripheral astigmatism is typically less in the nasal retina,^{4, 26, 29} the lower amount of astigmatism nasally accounts for the slightly better repeatability found at the 40° nasal retinal location in this study compared to that found at the 40° temporal retinal location. The asymmetry in astigmatism can be explained by angle lambda (the roughly 5° difference between the line of sight and the pupillary axis). Because measurements were made relative to the line of sight, central measurements were slightly temporal on the retina compared to the pupillary axis. Thus, measurements 40° temporal on the retina from the line of sight were actually more than 40° (closer to 45°) from the pupillary axis, which can explain the greater amount of astigmatism measured temporally on the retina than nasally in this study and by others.^{30, 31} That being said, the repeatability of defocus measurements at 30° was better temporally than nasally despite astigmatism being lower at the nasal location. Thus, while astigmatism likely plays a role in repeatability, other factors such as off-axis higher-order aberrations may also play a role.

The only other study that we are aware of that has evaluated off-axis, between-visit repeatability was by Lee et al. after subjects underwent orthokeratology treatment.¹⁵ Table 3 compares repeatability results for defocus from their study to the results of this study. In their study, the 95% LoA reached ± 3.00 D at 30° in the periphery, which is less repeatable than we found in normal eyes at 40° (± 0.88 D). The repeatability of off-axis, between-visit autorefraction in orthokeratology treated eyes is valuable for longitudinal studies examining the effects of orthokeratology on peripheral refraction because the influence of the corneal shape changes that occur with the oblate corneal shape changes caused by the procedure are taken into consideration. However, it is also important to know the off-axis repeatability of peripheral autorefraction in normal eyes that may be wearing either soft contact lenses or spectacles in which the prolate corneal shape is not altered by the optical correction. Based on the results of these two studies, it appears that peripheral autorefraction measurements made through the mid-peripheral cornea where orthokeratology causes rapid steepening is likely the cause of the reduced repeatability found in the study by Lee et al.

Subjects were instructed to point their nose at the fixation target to avoid small eye turns to eliminate the possibility that the extraocular muscles might distort eye shape and thereby alter peripheral refraction. Although head and eye positioning was visually verified by the examiner to ensure that the eye was in primary gaze prior to each set of measurements, it is possible that subtle eye turns may have still been present. That being said, a previous study found no significant difference between peripheral refraction measurements made using the eye and head turn methods;³² therefore, small residual eye turns that potentially remained while measurements were made in this study are unlikely to have significantly influenced peripheral refraction and its repeatability.

A limitation of this study is that between-visit repeatability was only evaluated in the horizontal meridian of the eye; repeatability was not assessed in the vertical meridian. Additional instrument modifications would be necessary to make measurements in the vertical meridian because the current instrument housing greatly limits the vertical field of view. We speculate that repeatability at each eccentricity in the vertical meridian would have been comparable to the repeatability found in the horizontal meridian because the same potential misalignment errors associated with off-axis measurements through an oval pupil in the horizontal meridian are also present when measuring in other meridians. Additionally, similar increases in the magnitude of astigmatism have been found out to 30 degrees in the vertical and horizontal meridians of the eye.⁹ That being said, future work should evaluate repeatability in meridians other than the horizontal meridian.

Another potential limitation of this study is that we did not investigate repeatability under non-cycloplegic conditions. Our goal was to determine the best repeatability that could be expected with this instrument in the absence of factors that might reduce repeatability such as accommodation. Non-cycloplegic central autorefraction has been shown to be less repeatable than cycloplegic central autorefraction,²⁷ and we anticipate that the same would be true with peripheral autorefraction. Under non-cycloplegic conditions, the subject's uncorrected refractive error combined with the target distance used can result in variable accommodative demands between subjects. Non-cycloplegic measurements also risk fluctuations in accommodation and thus variability in accommodative response, both of

which would be expected to reduce between-visit repeatability. If the goal of a study is to monitor for changes in peripheral refraction over time, cycloplegic measurements would minimize variability in the measurements made. The repeatability reported in this study represents the level of repeatability that one should expect under cycloplegic conditions in a longitudinal situation.

CONCLUSIONS

Peripheral autorefraction with the Grand Seiko WAM-5500 showed good repeatability, though repeatability did decrease as eccentric increased. While the repeatability of peripheral autorefraction measurements was not as good as that of central autorefraction, the between-visit repeatability of peripheral autorefraction was still superior to the previously reported repeatability of on-axis, cycloplegic subjective refraction. With clear knowledge of the repeatability of on- and off-axis cycloplegic autorefraction, peripheral measurements can be properly interpreted in longitudinal studies to determine whether treatments that induce myopic peripheral defocus in an attempt to slow the progression of myopia result in a meaningful influence on peripheral refraction.

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Figure 1.

Difference versus mean plot of central spherical-equivalent defocus (in diopters) measured at two separate visits. The solid line represents the mean difference between the two visits (bias), and the dashed lines represent the 95% limits of agreement.

Figure 2.

Difference versus mean plots for repeated measurements of peripheral spherical-equivalent defocus (in diopters) measured at (A) 20° nasally, (B) 20° temporally, (C) 30° nasally, (D) 30° temporally, (E) 40° nasally, and (F) 40° temporally on the retina at two separate visits. The solid lines represent the mean difference between the two visits (bias), and the dashed lines represent the 95% limits of agreement. (V1 = Visit 1 and V2 = Visit 2)

Table 1

Mean $\pm$ SD central and peripheral autorefraction values (in diopters) at each visit, bias, and repeatability.

	Retinal Location						
	40° Nasal	30° Nasal	20° Nasal	Central	20° Temporal	30° Temporal	40° Temporal
M							
Visit 1	-2.95 ± 1.91	-3.39 ± 1.79	-3.49 ± 1.70	-3.45 ± 1.42	-3.51 ± 1.49	-3.11 ± 1.67	-2.55 ± 2.01
Visit 2	-2.87 ± 1.95	-3.32 ± 1.77	-3.51 ± 1.67	-3.47 ± 1.41	-3.51 ± 1.53	-3.18 ± 1.67	-2.54 ± 2.01
Bias*	-0.08 ± 0.37	-0.07 ± 0.31	0.02 ± 0.21	0.02 ± 0.11	0.00 ± 0.18	0.06 ± 0.24	-0.02 ± 0.45
Repeatability [†]	± 0.73	± 0.60	± 0.42	± 0.21	± 0.36	± 0.47	± 0.88
J₀							
Visit 1	-0.92 ± 0.59	-0.53 ± 0.28	-0.13 ± 0.29	0.01 ± 0.19	-0.54 ± 0.29	-1.03 ± 0.36	-1.66 ± 0.59
Visit 2	-0.86 ± 0.61	-0.45 ± 0.28	-0.24 ± 0.24	0.02 ± 0.18	-0.51 ± 0.27	-1.05 ± 0.40	-1.70 ± 0.55
Bias*	-0.07 ± 0.36	-0.08 ± 0.23	0.11 ± 0.26	-0.01 ± 0.12	-0.04 ± 0.16	0.02 ± 0.22	0.04 ± 0.20
Repeatability [†]	± 0.71	± 0.45	± 0.51	± 0.23	± 0.32	± 0.44	± 0.39
J₄₅							
Visit 1	-0.35 ± 0.31	-0.21 ± 0.27	-0.16 ± 0.20	0.02 ± 0.19	0.14 ± 0.25	0.19 ± 0.33	0.25 ± 0.46
Visit 2	-0.32 ± 0.32	-0.21 ± 0.25	-0.20 ± 0.24	-0.01 ± 0.15	0.16 ± 0.26	0.18 ± 0.34	0.23 ± 0.48
Bias*	-0.04 ± 0.15	0.00 ± 0.13	0.04 ± 0.11	0.03 ± 0.09	-0.02 ± 0.08	0.01 ± 0.17	0.02 ± 0.19
Repeatability [†]	± 0.30	± 0.25	± 0.22	± 0.17	± 0.16	± 0.33	± 0.36

* Difference between visits (visit 1 – visit 2)

† 1.96 $\times$ standard deviation of mean difference between visits

Table 2

Mean $\pm$ SD relative peripheral refraction (RPR) in diopters at each visit, bias, and repeatability.

	Retinal Location					
	40° Nasal	30° Nasal	20° Nasal	20° Temporal	30° Temporal	40° Temporal
RPR						
Visit 1	0.49 $\pm$ 0.90	0.06 $\pm$ 0.79	-0.04 $\pm$ 0.58	-0.06 $\pm$ 0.41	0.33 $\pm$ 0.60	0.89 $\pm$ 1.19
Visit 2	0.59 $\pm$ 0.98	0.15 $\pm$ 0.71	-0.04 $\pm$ 0.56	-0.04 $\pm$ 0.40	0.29 $\pm$ 0.64	0.93 $\pm$ 1.21
Bias*	-0.10 $\pm$ 0.34	-0.09 $\pm$ 0.29	0.00 $\pm$ 0.19	-0.02 $\pm$ 0.16	0.04 $\pm$ 0.20	-0.04 $\pm$ 0.42
Repeatability [†]	$\pm$ 0.67	$\pm$ 0.57	$\pm$ 0.37	$\pm$ 0.31	$\pm$ 0.40	$\pm$ 0.82

* Difference between visits (visit 1 – visit 2)

[†] 1.96 $\times$ standard deviation of mean difference between visits

Table 3

Comparison of between-visit repeatability of central spherical equivalent autorefractometer measurements and relative peripheral refraction (RPR) measurements for the present study (normal eyes) and a previous study of orthokeratology-treated eyes.

	Between-Visit Repeatability* by Retinal Location						
	40° Nasal	30° Nasal	20° Nasal	Central	20° Temporal	30° Temporal	40° Temporal
Present Study (Normal Eyes)	±0.67	±0.57	±0.37	±0.21	±0.31	±0.40	±0.82
Orthokeratology Treated Eyes ^{1,5}	N/A [‡]	±1.78	N/A [‡]	±0.51	±1.45	±3.00	N/A [‡]

* 1.96 × standard deviation of mean difference between visits

[‡] Repeatability not evaluated at this location by Lee and Cho (2012)