The Effect of Phenylephrine and Cyclopentolate on Objective Wavefront Measurements

Mirko R. Jankov II, MD; Hans Peter Iseli, MD; Michael Bueeler, PhD; Paulo Schor, MD, PhD; Theo Seiler, MD, PhD; Michael Mrochen, PhD

ABSTRACT

PURPOSE: To investigate the impact of phenylephrine and cyclopentolate on wavefront refraction and fourth order spherical aberration C_{12}.

METHODS: This cohort study comprised 151 eyes with sphere up to −10.00 diopters (D) and cylinder −3.75 D. Aberrometry was performed using the ALLEGRO WAVE (WaveLight Laser Technologies AG, Erlangen, Germany) after instillation of phenylephrine 5% yielding objective phenylephrine refraction in accommodated steady-state, as well as after cyclopentolate 0.5% providing objective cyclopentolate refraction in non-accommodated state. Accommodation target fogging was turned off. Wavefront aberrations were expressed by Zernike expansion up to the sixth order, and paraxial curvature matching with Taylor series was used to calculate objective wavefront sphere.

RESULTS: Objective wavefront sphere was not influenced by pupil size. Eyes showed substantial accommodation after phenylephrine with a myopic shift of −0.66 D comparing objective to subjective manifest sphere ($r=0.942$, $P<.001$). Cycloplegic eyes behaved like a model eye, with a difference of −0.08 D between objective and subjective cycloplegic sphere ($r=0.976$, $P<.001$). C_{12} increased ten-fold from 4.0- to 7.0-mm pupil size, keeping the same sign. Comparing cyclopentolate with phenylephrine, the sign of C_{12} changed in a positive direction by an average $+0.124\pm0.109$ μm (range: −0.052 to +0.632 μm) at 7.0 mm, whereas the total higher order aberrations changed very little. A good correlation was found between C_{12} and the change in objective wavefront sphere between cyclopentolate and phenylephrine ($r=0.75$, $P<.001$).

CONCLUSIONS: Fogging of the accommodation target should be used for wavefront measurements. Weaker cycloplegic agents, such as tropicamide, may be used to ensure relaxed but not completely paralyzed accommodation, which would yield “manifest” aberration values close to the natural resting state. [*J Refract Surg*. 2006;22:472-481.]

The imprecision in determining accurate refraction provokes a number of problems in daily clinical routine, especially when planning refractive correction with spectacles or contact lenses. Moreover, if the purpose of evaluation is to plan a surgical refractive correction, the accuracy in doing so is crucial to minimize the need for enhancement procedures.[1]

Manifest refraction, in terms of spectacle sphere and cylinder, is a “traditional” subjective way of assessing the eye’s refraction and is still considered the gold standard.[2] It is usually performed with trial lenses under steady-state accommodation for distance, ie, without any mydriatic agents. Subjective cycloplegic refraction, in which the ciliary body is paralyzed and therefore in a completely relaxed state, is usually performed in younger patients or in hyperopic patients, where a significant amount of accommodation is expected, yielding more positive values for refraction when compared to the manifest refraction.[3]

With technological advancements in recent years, increased efforts have been invested in developing objective autorefractors with the intention of either complementing, or eventually substituting, the manual refraction process.[4] The recent surge of wavefront sensors, which can measure all of the eye’s aberrations, are an additional source used to objectively determine sphere and cylinder.[5] These wavefront sensors are considered precise in the determination of the eye’s refractive state, and a comparison with subjective refraction leads to the question of whether the “gold standard” is less reliable than the wavefront measurement.[2]

In principle, wavefront sensors, unlike autorefractors, re-

From Miloš Clinic Eye Hospital, Serbia and Montenegro (Jankov); Instituto de Visão, Escola Paulista de Medicina, Universidade Federal São Paulo, Brazil (Jankov, Schor); IROC - Institute of Refractive and Ophthalmic Surgery, Zurich, Switzerland (Iseli, Bueeler, Seiler, Mrochen); and Swiss Federal Institute of Technology, Zurich, Switzerland (Bueeler, Mrochen).

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Correspondence: Mirko R. Jankov II, MD, Miloš Clinic Eye Hospital, Radoslava Grujica 25, 11000 Belgrade, Serbia and Montenegro. Phone/Fax: 381 11 245 5759; E-mail: visioncare@mac.com

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TABLE

Demographic Data of 151 Eyes That Underwent Measurement of Wavefront Refraction Using Phenylephrine and Cyclopentolate

	Mean±SD	Min	Max
Age (y)	33±9	18	57
Mean corneal curvature (K)	43.95±1.46	39.7	47.6
Mean corneal astigmatism (D)	1.20±0.68	0.10	3.30
Corneal asphericity (Q-value)	−0.19±0.08	−0.42	0.00
Corneal thickness (μm)	547±33	415	624
Mesopic pupil size (mm)	5.70±0.70	4.00	8.00
Subjective manifest sphere (D)	−2.91±2.10	−10.00	0.00
Subjective manifest cylinder (D)	−0.94±0.74	−3.50	0.00
Subjective cycloplegic sphere (D)	−2.68±2.13	−10.00	1.00
Subjective cycloplegic cylinder (D)	−0.98±0.73	−4.00	0.00

quire large pupils to assess higher order ocular aberrations, as such aberrations appear only with pupil diameters ⩾4.0 mm.[6] The fact that higher order aberrations are mainly relevant in larger pupils leads to an unpleasant dilemma. On one hand, large pupils are needed to determine the higher order aberrations that are of relevance in scotopic or mesopic conditions. On the other hand, pharmacologic dilation leads to using mydriatic agents, which also have a certain influence on accommodation and optical performance, which might lead to false measurements. An additional problem arises from the fact that the objective refraction can be derived in different ways from the wavefront measurement. Consequently, wavefront refraction can be represented in various ways, which might lead to differences as large as 0.75 diopters (D), as described by Thibos et al.[2] Surprisingly, their work also demonstrated a good correlation between the subjective refraction and objective refractive representations that are based on paraxial optics such as Taylor sphere and cylinder. Thus, we chose this type of representation for our analysis.

The purpose of this study was to investigate the impact of phenylephrine and cyclopentolate, which characterize two different accommodation states, on wavefront refraction and fourth order spherical aberration. This study was intended to find a basis for a standardized medication regime for clinical wavefront sensing in corneal laser surgery.

MATERIALS AND METHODS

Eighty-one myopic patients (43 men and 38 women) (151 eyes, 79 right and 72 left) who presented for refractive surgery at our clinic between June 2002 and May 2003 were included in this cohort study. Mean uncorrected visual acuity (UCVA) was 20/180 (range: 20/20 to 20/400) and best spectacle-corrected visual acuity (BSCVA) was 20/19 (range: 20/15 to 20/60). Other demographic data can be found in the Table.

Exclusion criteria were 1) active ocular disease or a history of keratitis; 2) refractive cylinder up to −3.75 diopters (D); 3) active systemic disease such as diabetes mellitus; and 4) pregnancy. If the patient wore contact lenses, 2-week abstinence for soft contact lenses and 4-week abstinence for toric and rigid contact lenses was required prior to evaluation.

Preoperative clinical investigation included UCVA, BSCVA, subjective manifest and subjective cycloplegic refraction, slit-lamp examination with fundus evaluation, corneal topography (Topolyzer; Oculus, Wetzlar, Germany), and ultrasonic pachymetry (Pac Scan 300P; Sonomed, Lake Success, NY).

The examination procedure is shown schematically in Figure 1. After evaluation of UCVA, manifest refraction, and BSCVA, two drops of phenylephrine 5% with an interval of 10 minutes are instilled. Thirty minutes later, subjective manifest refraction is confirmed, ensuring that no significant change has occurred in accommodation compared to the values prior to dilatation.[7] A series of four measurements at a steady-state accommodation were carried out by a wavefront aberrometer ALLEGRO WAVE (WaveLight Laser Technologie AG, Erlangen, Germany), which served as the basis for objective phenylephrine wavefront refraction, as described below. Immediately afterwards, two drops of cyclopentolate 0.5% were applied with an interval of 10 minutes, and 30 minutes later subjective cycloplegic refraction was measured.

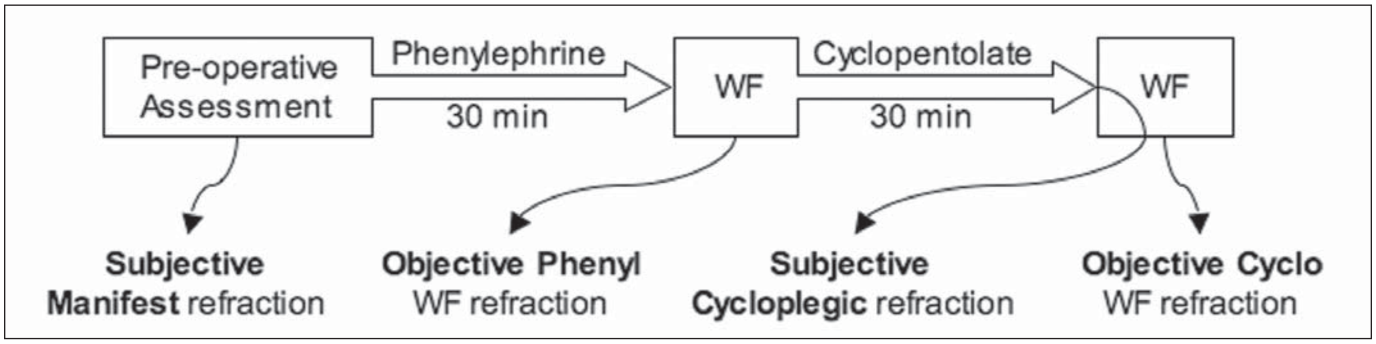

Figure 1. Schematic of the examination procedure.

Finally, four additional measurements were acquired by the wavefront aberrometer in this non-accommodated state, which were used for calculation of objective cyclopentolate wavefront refraction.

Wavefront sensing was performed using the ALLEGRO WAVE based on the principles of Tscherning aberrometry. Details of the measuring device have been reported elsewhere.[8,9] Basically, this ray tracing method uses the mathematical analysis of a retinal spot pattern captured by a video camera. From the deviations of the spot positions to their ideal position the first derivative of the wavefront was calculated. Wavefront aberrations were expressed in 27 Zernike coefficients up to the sixth order, as proposed by the Optical Society of America VSIA taskforce[10] and separately exported to be pre-analyzed in the commercially available spreadsheet software Excel (Microsoft, Redmond, Wash).

The accommodation target was preset to compensate for the subjective refraction, as predetermined by the wavefront measurement, while fogging of the accommodation target was turned off during wavefront sensing. Thus, the patient was able to see the fixation target to assure centration with respect to the line of sight but the accommodation target did not additionally motivate the patient to relax his or her accommodation to the far point.

Repeatability Test

The average of four consecutive wavefront measurements was used in our calculations, as suggested by the manufacturer rather than using only a single measurement. For each set of four measurements, confidence interval (CI) with significance level of 95% for C_4 was calculated; mean CI and standard deviation (SD) were determined, and only the eyes that had a CI within 3 SD from the mean CI of each group were considered eligible for the study, eliminating the measurements with insufficient repeatability. Fifteen eyes were excluded because of non-fulfillment of the previous condition in either phenylephrine or cyclopentolate measurements, totaling 151 eligible eyes. All Zernike coefficients were then averaged, normalized, and expressed in microns.

Calculation of Objective Wavefront Refraction

Total wavefront aberrations (W) were expressed by Zernike expansion

$$W(x,y) = \sum_{i=0}^{27} C_i Z_i(x,y)$$

where C_i = Zernike coefficients and Z_i = Zernike polynomials. Zernike coefficients for this study were calculated for pupil diameters of 4.0 and 7.0 mm.

Manifest sphere and dilated (cycloplegic) sphere were recalculated from 13-mm vertex distance to corneal plane using the following formula:

$$Sph_c = \frac{Sph_s}{1-d\cdot Sph_s}$$

where Sph_c and Sph_s represent sphere (in diopters) at the corneal and spectacle level, respectively, and d represents the vertex distance (in meters).

Paraxial curvature matching method (Taylor series) was used to calculate objective wavefront sphere, as it is shown to more accurately represent refractive status of the eye than the method of least-squares fitting.[2,11] In this case, Zernike terms for defocus C_4 and astigmatism Zernike terms C_3, C_5, as well as for the spherical aberration terms (C_{12} and C_{24}) and higher order astigmatism (C_{11} and C_{13} and C_{23} and C_{25}) are all used to calculate the objective sphere and cylinder for a given pupil radius R:

$$\text{Sph} = -\left(W_4 + W_6 + \frac{Cyl}{2}\right) \quad Cyl = -2\sqrt{(W_6 - W_4)^2 + W_5^{\,2}}$$

$$W_4 = \frac{2\sqrt{3}\cdot C_4 + \sqrt{6}\cdot C_5 - 6\sqrt{5}\cdot C_{12} - 3\sqrt{10}\cdot C_{13} + 12\sqrt{7}\cdot C_{24} + 6\sqrt{14}\cdot C_{25}}{16R^2}$$

$$W_5 = \frac{2\sqrt{6}\cdot C_3 - 6\sqrt{10}\cdot C_{11} + 12\sqrt{14}\cdot C_{23}}{16R^2}$$

$$W_6 = \frac{2\sqrt{3}\cdot C_4 - \sqrt{6}\cdot C_5 - 6\sqrt{5}\cdot C_{12} + 3\sqrt{10}\cdot C_{13} + 12\sqrt{7}\cdot C_{24} - 6\sqrt{14}\cdot C_{25}}{16R^2}$$

Statistical tests used in the analysis were paired Stu-

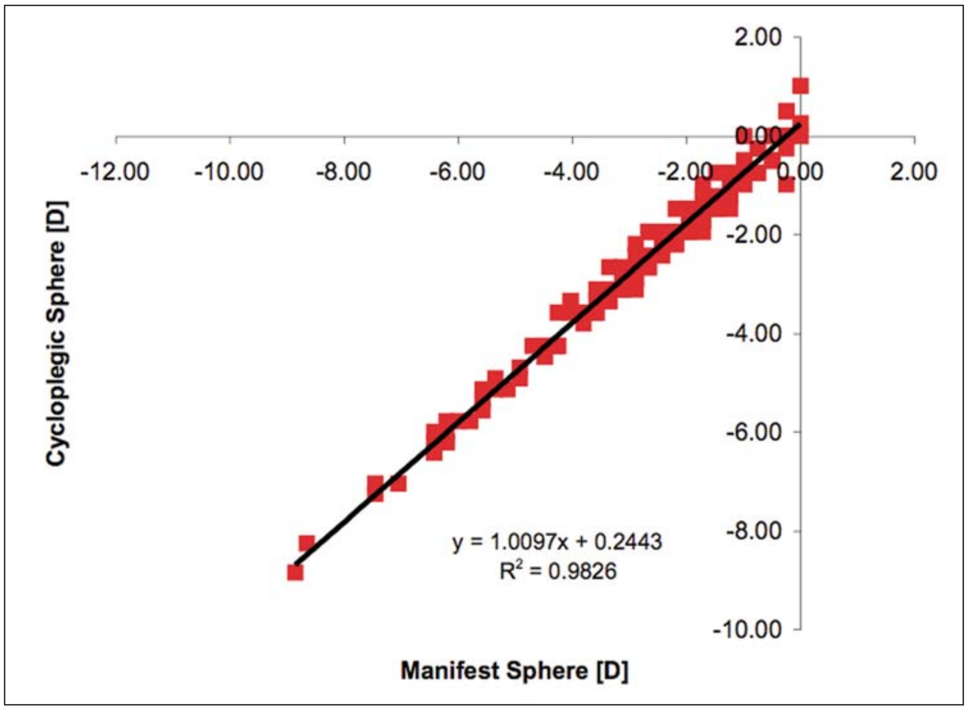

Figure 2. Comparison of subjective cycloplegic vs manifest sphere.

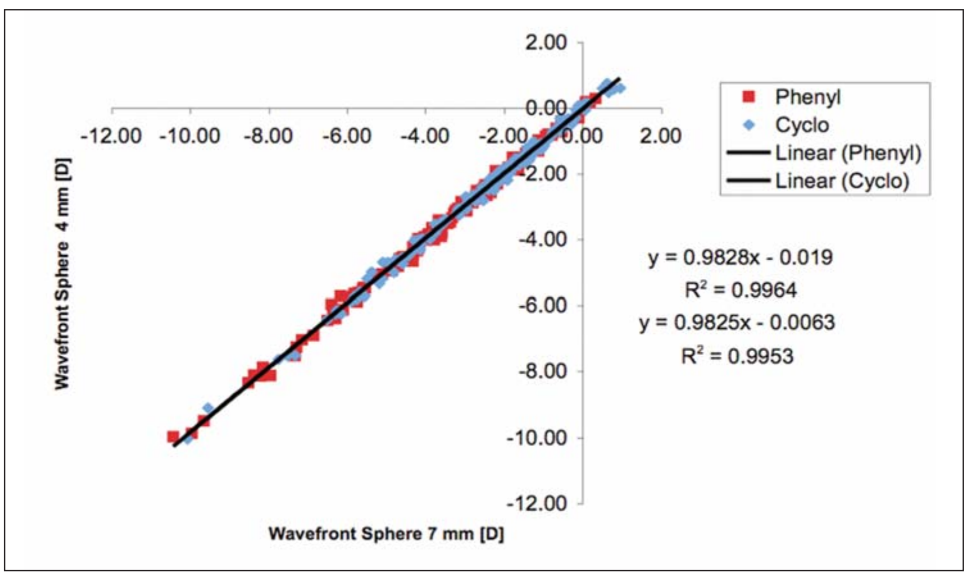

Figure 3. Comparison of objective wavefront spheres for 4.0-mm vs 7.0-mm pupil size.

dent *t* test for testing the means and Pearson correlation for testing the linear relationship between variables.

RESULTS

SUBJECTIVE MANIFEST VS SUBJECTIVE CYCLOPLEGIC REFRACTION

Cycloplegia resulted in a hyperopic shift. Subjective cycloplegic sphere changed by +0.24 D (less myopic) compared with subjective manifest sphere (Fig 2), which shows a statistically significant difference ($P<.001$, paired Student *t* test) and a significant correlation (r=0.99, $P<.001$, Pearson correlation).

INFLUENCE OF PUPIL SIZE

Pupil size was irrelevant when calculating objective wavefront sphere. Figure 3 demonstrates a significant correlation (r=0.998, $P<.001$, Pearson correlation) but no statistical difference when comparing objective wavefront calculated sphere between 7.0-mm and 4.0-mm pupil size after phenylephrine (mean: −0.04±0.13 D, range: −0.48 to +0.32 D, P=.864, independent Student *t* test) and after cyclopentolate (mean: −0.04±0.14 D, range: −0.46 to +0.32 D, P=.886, independent Student *t* test).

PHENYLEPHRINE WAVEFRONT REFRACTION VS MANIFEST SPHERE (4-MM PUPIL SIZE)

Eyes had substantial accommodation during wave-

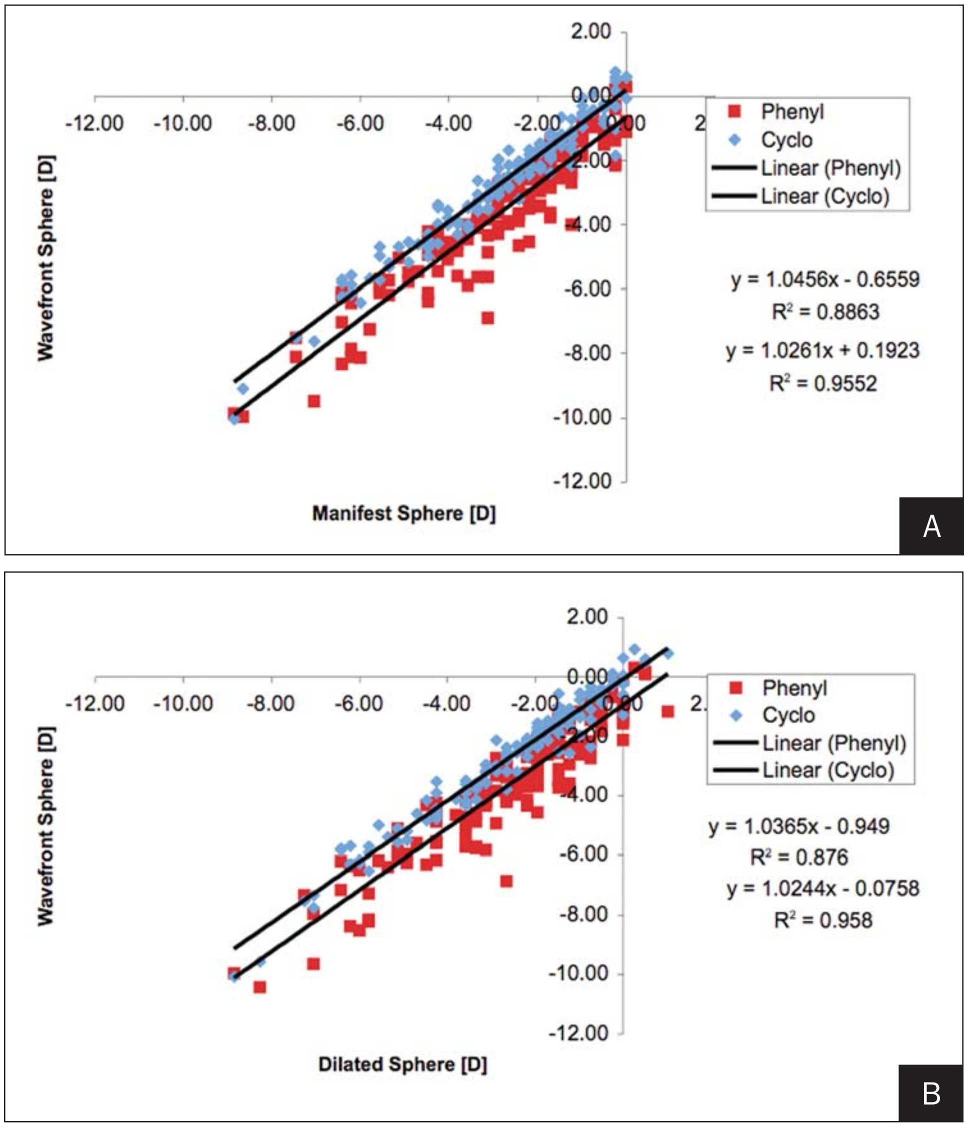

Figure 4. Comparison between **A)** objective phenylephrine and cyclopentolate wavefront sphere vs subjective manifest sphere and **B)** comparison between objective phenylephrine and cyclopentolate wavefront sphere vs subjective cycloplegic sphere.

front sensing after dilation with phenylephrine, which led to a myopic shift of the refractive sphere. Objective phenylephrine wavefront sphere for 4.0- and 7.0-mm pupil size changed by −0.66±0.73 D (more myopic) compared to subjective manifest sphere (*P*<.001, paired Student *t* test; r=0.942, *P*<.001, Pearson correlation) (Fig 4A) and by −0.95±0.76 D (more myopic) compared to subjective cycloplegic sphere (*P*<.001, paired Student *t* test; r=0.93, *P*<.001, Pearson correlation) (Fig 4B).

Cyclopentolate Wavefront Refraction vs Cycloplegic Sphere (7.0-mm Pupil Size)

Human eyes paralyzed by cycloplegia behaved similarly to a geometric optical model eye during the measurements. Objective cyclopentolate wavefront sphere changed by +0.19±0.45 D (less myopic) compared to subjective manifest sphere (*P*<.001, paired Student *t* test; r=0.976, *P*<.001, Pearson correlation) (see Fig 4A) and by −0.08±0.42 D (more myopic) compared to subjective cycloplegic sphere (*P*=.029, paired Student *t* test; r=0.976, *P*<.001, Pearson correlation) (see Fig 4B).

Cycloplegic vs Phenylephrine Spherical Aberration

Sign reversal was observed in fourth order spherical aberration. The magnitude of spherical aberration C_{12} increased ten-fold from 4.0- to 7.0-mm pupil size, while keeping the same sign, ie, always negative after phenylephrine and always positive after cyclopentolate (Fig 5). With a 7.0-mm pupil, the sign of spherical aberration changed in the positive direction by an average of +0.124±0.109 µm (range: −0.052 to +0.632 µm) from −0.026±0.189 µm (range: −0.718 to +0.473 µm) after phenylephrine to +0.098±0.148 (range: −0.314 to +0.472 µm) after cyclopentolate. At

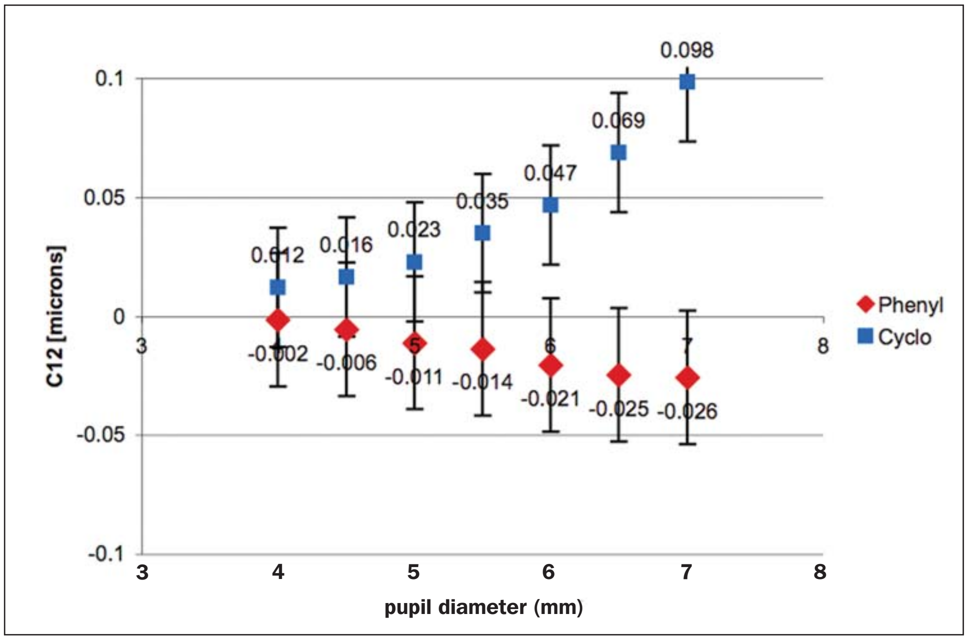

Figure 5. Change in fourth order spherical aberration C_{12} with the increase in pupil size.

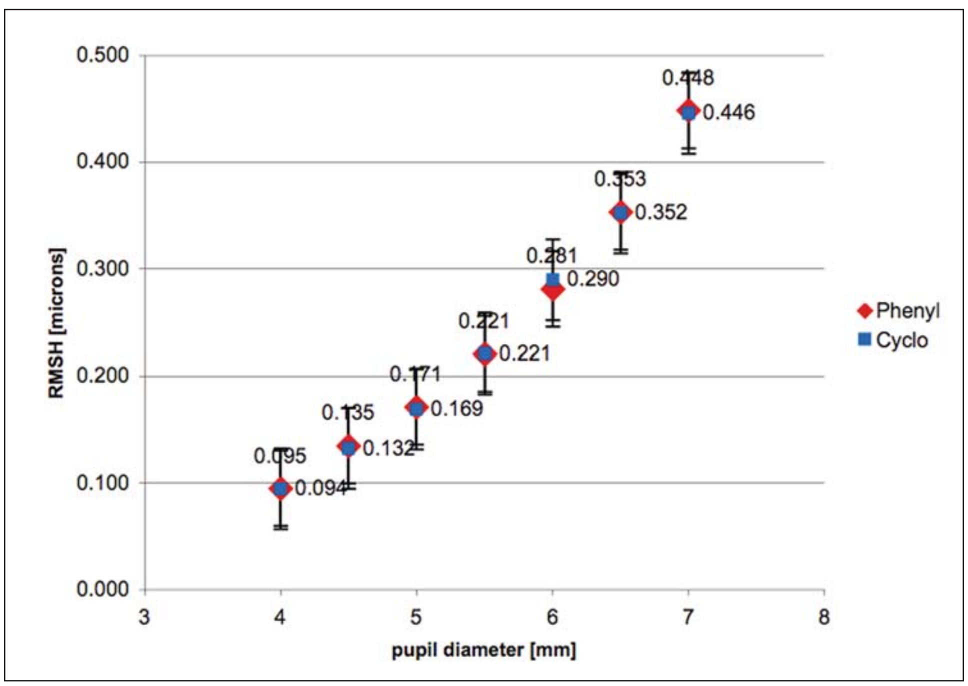

Figure 6. Change in higher order aberrations expressed as root-mean-square error (RMSH) with the increase in pupil size.

the same time, the total higher order aberrations, characterized by root-mean square error (RMSH), changed little, from 0.448±0.148 µm (range: 0.180 to 0.993 µm) after phenylephrine to 0.446±0.165 µm (range: 0.149 to 1.122 µm) after cyclopentolate (Fig 6).

Correlation Between Wavefront Sphere and Spherical Aberration

Fourth order spherical aberration was affected depending on the accommodation status during the measurement. A statistically significant correlation was noted between the change in spherical aberration (7.0-mm pupil) between cyclopentolate and phenylephrine versus the change in objective wavefront sphere between cyclopentolate and phenylephrine (r=0.75, $P<.001$, Pearson correlation), as seen in Figure 7, as well as with the change between dilated and manifest sphere (r=0.322, $P<.001$, Pearson correlation), although somewhat weaker. The change in spherical aberration at a 7.0-mm pupil between cyclopentolate and phenylephrine was also statistically correlated to the value of C_{12} at the 7.0-mm pupil after phenylephrine (r=−0.625, $P<.001$, Pearson correlation), showing that eyes with a more negative value of C_{12} after phenylephrine have

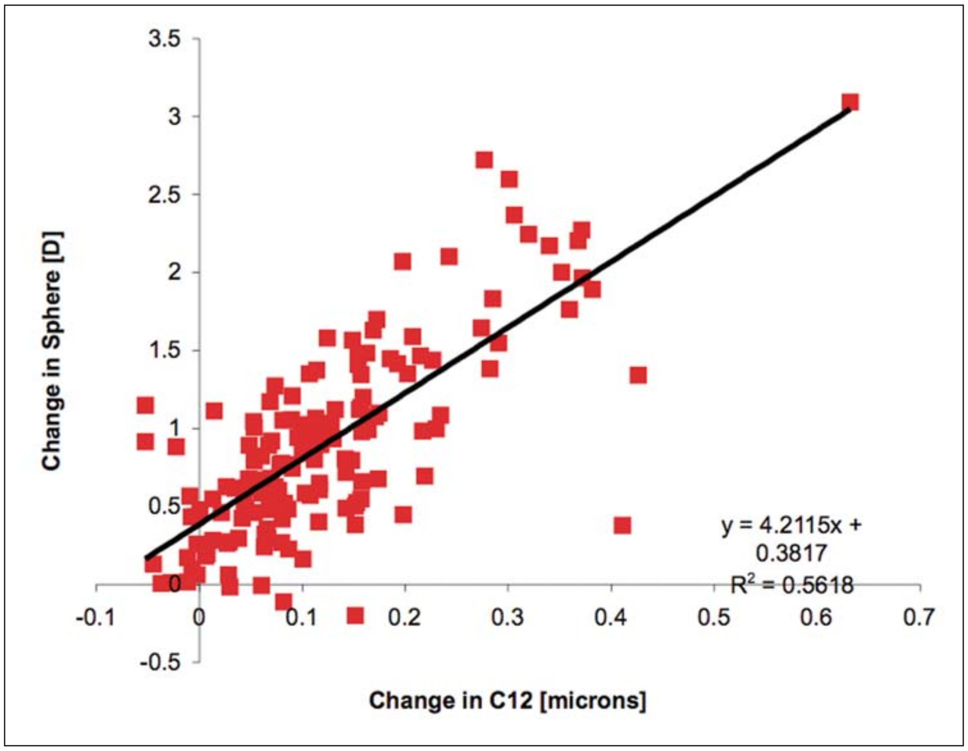

Figure 7. Change in objective wavefront sphere (cyclopentolate − phenylephrine) vs change in fourth order spherical aberration C_{12} at 7.0 mm (cyclopentolate − phenylephrine).

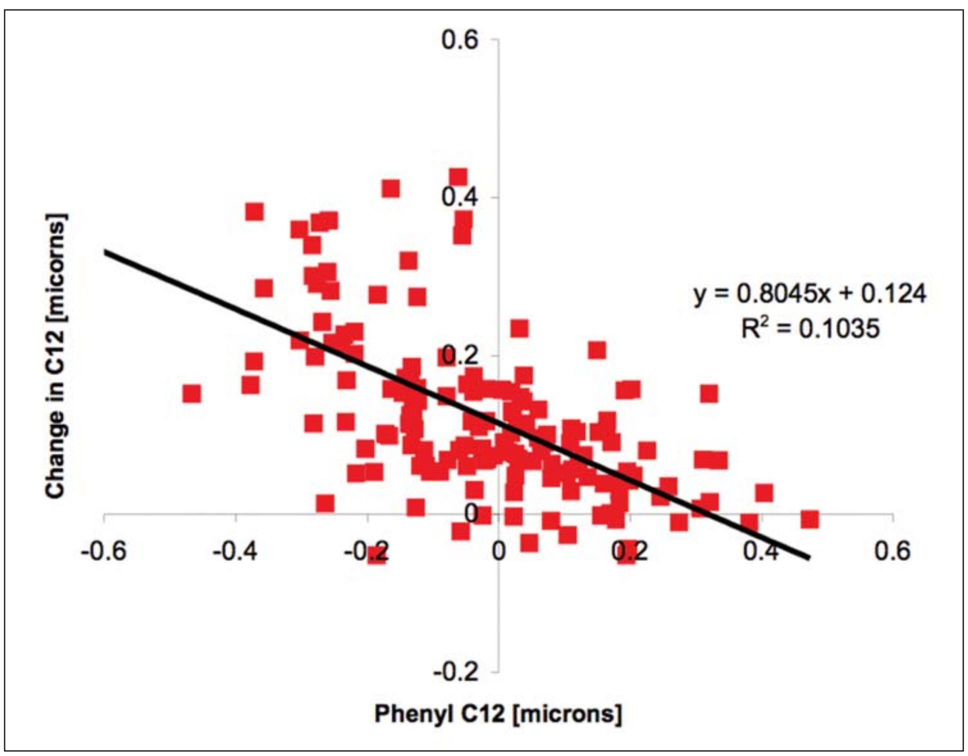

Figure 8. Value of fourth order spherical aberration C_{12} after phenylephrine vs change in C_{12} at 7.0 mm (cyclopentolate − phenylephrine).

a larger positive shift of their spherical aberration after cyclopentolate (Fig 8).

DISCUSSION

The accommodation status and the pupil size are known to be of relevance during wavefront sensing. It is believed that phenylephrine dilates the pupil with minimal effect on accommodation, whereas cyclopentolate reduces accommodation.[3,7] Our results have shown that even the sphere alone may be misinterpreted due to some “apparatus” accommodation (eg, the accommodation target may have not been “accommodative neutral") within the wavefront-sensing device. The higher order aberrations, such as fourth order spherical aberration, are also affected.

The eye's normal functional state for distance is tonic (steady-state) accommodation. This means that, even for an object in infinity, a certain amount (0.25 to 0.50 D of accommodation) is present due to the balance between the sympathetic and parasympathetic innervation.[3] It occurs even in the absence of a stimulus (so-called "dark focus"), and its effect puts the focus of a distant object slightly in front of the retina, turning the eye slightly myopic. A completely relaxed accommodation happens only by blocking the innervation, usually by using anti-cholinergic (cycloplegic) drugs, which paralyze the accommodative capability of the ciliary muscle. In our study, as expected, subjective cycloplegic sphere differed by +0.24 D (less myopic) from the subjective manifest sphere, which is due to the relaxation of tonic (steady-state) accommodation present even for distance viewing.

The objective wavefront sphere for 4.0- and 7.0-mm pupil size after phenylephrine and cyclopentolate was not significantly different (see Fig 3), which shows that either of the two can be used to calculate the objective wavefront sphere when using the paraxial curvature matching method (Taylor series). Knowing that the subjective manifest refraction was measured with a small pupil, whereas subjective cycloplegic refraction was measured with a large one, we compared them with objective wavefront spheres at 4.0 and 7.0 mm, respectively.

Wavefront aberrometers use an accommodation target to align the eye's line of sight to the camera axis. Considering the fact that the target distance is significantly shorter than 6 m, which is defined to be distance viewing, it is critical to ensure that the accommodation is completely relaxed, ideally achieving physiological relaxation of accommodation to the resting tonus. If not, the wavefront device will measure different amounts of accommodation, which will result in so-called "apparatus" myopia. The usual solution for this problem is "fogging" of the accommodation target (eg, blurring by additional lenses, driving the target further away, etc) to relax accommodation. In our study, in which the fogging was deliberately turned off, objective phenylephrine wavefront sphere differed by −0.66 D (more myopic) compared to subjective manifest sphere, which suggested that patients were accommodating during the measurements.

On the other hand, objective cyclopentolate wavefront sphere changed by only −0.08 D (more myopic) when compared to the subjective cycloplegic sphere; this difference was, however, statistically significant. Under cycloplegia, as patients cannot accommodate, and thus the function of "fogging" of the accommodation target inside the aberrometer becomes less critical, the wavefront aberrometer reads the values of pure refractive sphere for relaxed accommodation, which were similar to the subjective cycloplegic sphere. Under cycloplegia we observed that the human eye behaved similarly to a geometric optical model eye during the measurement, as it lost its ability to accommodate. This permitted us to compare the subjective cycloplegic refraction with the objective cycloplegic wavefront refraction. As a result, we found that the wavefront sphere calculated on the basis of Taylor modes represents the subjective refraction with high accuracy. This finding supports the findings of Thibos et al[2] and leads us to observe that the eye is following the paraxial optics to a high degree. Reasons for this might be the Stiles–Crawford effect and the density distribution of cones within the fovea.

Accommodation theory states that a change in the power of the crystalline lens is a result of its change in shape,[12] which can be measured through change in the spherical aberration C_{12}. Figure 5 clearly shows a tenfold increase in spherical aberration with the increase in pupil size, while still keeping the same sign, which is in accordance with the findings that higher order aberrations are more pronounced in larger pupils.[6] It has been shown that the average spherical aberration in the human population is between +0.1 and +0.15 µm for 6-mm pupil diameter,[13-17] with a standard deviation as large as ±0.133 µm.[14-16] Spherical aberration is also shown to turn more negative with the increase of accommodation effort, although not necessarily crossing zero.[16,17] Our study showed the average negative value for spherical aberration for a 7.0-mm pupil after phenylephrine to be −0.026±0.189 µm (range: −0.718 to +0.473 µm), while presenting with +0.098±0.148 µm (range: −0.314 to +0.477 µm) after cyclopentolate, the latter being in accordance with the values encountered in the literature for the relaxed eye. One can therefore postulate that aberrometric measurements in our study after phenylephrine without fogging have actually been carried out in a partially accommodated state of the eye, which rendered spherical aberration more negative than encountered after cyclopentolate.

Although the average difference between spherical aberration after phenylephrine and cyclopentolate of 0.124 µm by itself would probably not be clinically significant, corresponding to a dioptric equivalent of approximately 0.1 D, there are two aspects that drew our attention pointing out the importance of this change: first, there is a large individual difference in the change of spherical aberration, with a 95% reference range of as much as 0.404 µm, which emphasizes the need for close follow-up of the change in every individual case; and second, interactions between single-mode aberrations with a fixed level of RMS and a low amount of aberrations are shown to have an important clinical impact of up to two-line changes in high-contrast logMAR visual acuity.[18] Marsack et al[18] kept total RMS wavefront error constant at 0.25 µm over a 6-mm pupil (a fixed equivalent dioptric error of 0.19 D) and varied the relative proportion of the wavefront error by making different combination pairs of single Zernike modes. Their findings demonstrate that the manner in which the Zernike modes are combined significantly impacts measured visual acuity in a way that RMS wavefront error and equivalent dioptric error cannot predict.

The probable reason is that RMS wavefront error specifies only the standard deviation of the wavefront error over the pupil and not how this wavefront error was distributed within the pupil and its resulting effect on the point spread function in the spatial domain. This topic is nonetheless beyond the scope of our study. Interestingly, however, higher order aberrations expressed in RMSH were virtually unchanged in our study, from 0.448 to 0.446 µm, despite an important change in spherical aberration. This finding shows that whenever there is a change in sign of a particular aberration term but not in its absolute value, RMSH is unaffected by that change. We therefore agree that RMSH is not a good measure of higher order aberrations, especially to quantify the effects of low levels of aberration on visual acuity.

In this study, the change in spherical aberration correlated with the change in the objective wavefront sphere between phenylephrine and cyclopentolate. This shows that the more the crystalline lens changes its shape between steady-state accommodation (after phenylephrine only) and the relaxed accommodation (after cyclopentolate), the more its spherical power under two accommodative states will vary. Moreover, statistically significant correlation between the spherical aberration in steady-state accommodation and its change when the accommodation is relaxed shows that the eyes with a more negative value of C_{12} after phenylephrine tend to show a larger shift towards positive spherical aberration after cyclopentolate than those with a less negative baseline C_{12}. It is evident that spherical aberration is affected by the accommodative status during the measurement. One could conclude that patients who present with higher values of spherical aberration should be carefully examined for their subjective and objective refraction, as unexpected refractive outcome may occur.

This could mean that, if spherical aberration measured under cycloplegic conditions (relaxed accommodation, positive C_{12}) should be corrected by means of photorefractive surgery, and the eye re-establishes its tonic accommodation with the lens reassuming its less convex shape, the opposite spherical aberration may occur. In addition, He et al[17] suggested that the optical quality of the eye is best at the resting point of accommodation, and that aberrations increase for targets closer and farther from the eye. Thus, some of the aberration that the lens can partially compensate will most probably be overestimated and unnecessarily corrected, which would be "uncovered" only after the eye re-establishes its tonus accommodation.

The results showed that the dilemma about acquisition and interpretation of objective wavefront refraction still exists. Large pupils are necessary and appropriate for wavefront measurements to correctly detect higher order aberrations. On one hand, dilation with phenylephrine preserves the natural accommodation (or at least does not change it significantly), which make it perfect for detecting the "manifest" aberrations. Our results, however, show that lower order aberrations, mainly sphere, are not read correctly, because a certain amount of accommodation is taking place during measurements. On the other hand, accommodation was successfully blocked after cyclopentolate, but the value of spherical aberration was distorted significantly, leading us to believe that some aberrations measured this way might actually be overestimated. To avoid such problems, we suggest that fogging of accommodation target be used at all times while performing wavefront measurements. In addition, as a compromise, a weaker cycloplegic agent, such as tropicamide, could be used to relax accommodation without completely paralyzing it, thus yielding wavefront aberration values as close as possible to the natural resting state of the eye.

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