Impact on visual quality of higher-order aberrations related to amblyopic eyes

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1. Abstract

The purpose of this study was to assess the effect of higher order aberrations (HOAs) of idiopathic amblyopic eyes on their visual performance. To assess the visual function, an adaptive optics visual simulator (crx1, Imagine Eyes, France) was used to simulate the wavefront aberration pattern of normal and amblyopic eyes. Visual acuity (VA) for high (100%), medium (50%), and low (10%) contrast, and contrast sensitivity (CS) at 10, 20 and 25 cycles per degree (cpd) were measured for both groups. The Modulation Transfer Function (MTF) and the Point Spread Function (PSF) were also computed for both groups. Moreover, all measures were taken for 3- and 5.5-mm pupils.

No statistical significant differences were found in VA and CS between both groups at any contrast, spatial frequency and pupil size analysed (P>0.01). These values were similar between both groups. Mean logMAR VA for a 3 mm pupil was -0.11±0.04, -0.06±0.06 and 0.17±0.07 for 100%, 50% and 10% contrast levels, respectively. At 5.5 mm pupil these values were -0.06±0.04, 0.00±0.05 and 0.21±0.06 at 100%, 50% and 10% contrast levels, respectively. Mean CS for a 3 mm pupil was 1.9±0.2, 1.2±0.15 and 0.9±0.1 for 10, 20, and 25 cpd, respectively. For a 5.5 mm pupil, CS was 1.4±0.2, 0.9±0.2 and 0.6±0.2 for 10, 20, and 25 cpd respectively. MTFs and PSFs were comparable for both groups at 3 and 5.5mm.

Finally, no differences in the visual performance between normal and amblyopic eyes were found. This confirms that HOAs alone do not affect the visual function of idiopathic amblyopic eyes.

1. Resumen

El objetivo de este estudio fue evaluar el efecto de las aberraciones de alto orden (HOA), de ojos con ambliopía idiopática, en la función visual. Para ello se utilizó un simulador visual de óptica adaptativa (crx1, Imagine Eyes, France) para simular el patrón del frente de onda de ojos ambliopes y normales. Se midió la agudeza visual
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(AV) para alto (100%), medio (50%) y bajo (10%) contraste; y la sensibilidad al contraste (SC) para 10, 20 y 25 ciclos por grado (cpg). Ambas métricas, la AV y la SC, se midieron para los dos grupos considerados (ojo normal y ambliope). Además, la Función de Transferencia de Modulación (MTF) y la Función de Esparcimiento de Punto (PSF) también se calcularon para ambos grupos. Todas estas medidas se tomaron para 3- y 5,5-mm de diámetro pupilar.

Los resultados obtenidos revelan que no hay diferencias estadísticamente significativas en la AV y SC entre los dos grupos evaluados, para ningún contraste, frecuencia espacial y tamaño pupilar estudiados (P>0,01). La AV logMAR media para 3 mm de pupila fue -0,11±0,04, -0,06±0,06 and 0,17±0,07 para 100%, 50% y 10% de contraste, respectivamente. Para 5,5 mm de diámetro pupilar, los valores fueron -0,06±0,04, 0,00±0,05 y 0,21±0,06 para 100%, 50% y 10% de contraste, respectivamente. La SC media para 3 mm de pupila fue 1,9±0,2, 1,2±0,15 y 0,9±0,1 para 10, 20, y 25 cpd, respectivamente. Para 5,5 mm de diámetro pupilar, la SC fue 1,4±0,2, 0,9±0,2 y 0,6±0,2 para 10, 20, y 25 cpd respectivamente. Las MTFs y PSFs fueron comparables para ambos grupos para 3 y 5,5 mm.

Finalmente, no existen diferencias en la función visual entre ojos normales y ambliopes. Esto confirma que solo las HOAs no afectan a la función visual de ojos con ambliopía idiopática.
2. Introduction

The mechanism for idiopathic amblyopia is uncertain. Some investigators have postulated that it might be caused by transient anisometropia during infancy\textsuperscript{1,2}. However, with the introduction of wavefront analysis technology, some authors suggest\textsuperscript{3-5} that differences in higher order aberrations (HOAs) between the two eyes might trigger the development of amblyopia. For instance, Prakash et al.\textsuperscript{4} reported a case report of a patient with idiopathic amblyopia, where they did not find stimulus deprivation, strabismus, unequal refractive error, or organic cause which explain the difference in the best corrected visual acuity (VA) between normal and amblyopic eyes. The presence of crowding phenomenon, lower contrast sensitivity (CS), and poorer pattern visually evoked potentials in the amblyopic eye, with reduced stereoacuity helped them to establish the diagnosis of amblyopia. Microtropia, as a possible cause of unexplained amblyopia, was ruled out by a normal prism test and Bagolini glasses. The only difference that they found in this patient, with idiopathic amblyopia, was the wavefront aberrations between the normal and the amblyopic eye. In the same study\textsuperscript{4}, these authors suggested that between-eye difference in the wavefront profiles could have resulted in the one eye gaining dominance and the other eye becoming amblyopic. However, they thought that it could be possible that in their patient’s infancy he had a transient anisometropia, which resolved after the differential growth of the two eyes, leaving residual amblyopia.

After this case report, Prakash et al\textsuperscript{6} studied the effect of HOAs in amblyopic eyes. They measured the HOAs in seventeen children with idiopathic amblyopia and normal ocular development. No significant differences were found in mean Zernike coefficients between normal and amblyopic eyes. However, using a stepwise regression analysis, they obtained different HOAs patterns for normal and amblyopic eyes. This argument was used to explain the reason why there is a different visual function
between amblyopic and fellow eyes. Finally, they concluded that it seems a strong possibility that a subset of idiopathic amblyopia could be associated with loss of symmetry in wavefront patterns between the two eyes. Then, it would be interesting to analyse the effect of HOAs, related to amblyopic eyes, on the visual performance.

In the present study, I evaluated the visual performance of idiopathic amblyopic eyes through their HOAs pattern. In order to check how amblyopic HOAs pattern affect the visual performance, visual outcomes were compared to normal eyes. To assess visual performance, CS and VA for different contrast levels, for 3- and 5.5-mm pupil sizes, were determined applying both normal and amblyopic eyes HOAs patterns. To carry out this study, an adaptive optics (AO) visual simulator was used. In order to assess the optical quality in both groups, the Modulation Transfer Function (MTF) and the Point Spread Function (PSF) were computed. Moreover, this is, to the best authors’ knowledge, the first study that allows a direct comparison of the visual performance achieved with different ocular conditions in the same patient.
3. Patients and Methods

3.1. Subjects

Seven individuals, aged from 21 to 30 years, were included in this study. The mean age was 25.14±3.13 years. The subjects included in this study have experience in psychophysical experiments. Spherical refractive errors ranged between -2.00 and 0.00 diopters (D) with astigmatism <0.25 D. The mean spherical equivalent was -0.42±0.60 D. They had clear intraocular media and no known ocular pathology. Patients with a pupil size smaller than 5.5 mm in dark conditions were excluded since all measurements were carried out without the instillation of any mydriatic eye drop.

The tenets of the Declaration of Helsinki were followed. Informed consent was obtained from each participant after verbal and written explanation of the nature and possible consequences of the study. The protocol received institutional review board approval.

3.2. Adaptive Optics Visual Simulator

The crx1 AO system (Imagine Eyes, Orsay, France) is the visual simulator used during this study. It comprises two basic elements: a Hartmann-Shack wavefront sensor and a correcting device. The optical system conjugates the exit pupil plane of the individual with the correcting device, the wavefront sensor, and the artificial pupil. The Hartmann-Shack wavefront sensor has a square array of 1024 lenslets. The wavefront aberration measurements are made at 850 nm. The deformable mirror is a correcting system composed of 52 independent magnetic actuators used either to partially or totally correct the aberrations up to the 5th order (18 Zernike coefficients) and to add different values of aberrations (up to 4th order). The control of the deformable mirror surface is accomplished by a commercially available program (HASO, Imagine Eyes), which reshapes the deformable mirror from its normal flat surface to the desired shape.
The observer viewed visual tests generated on a micro-display through the AO system and the artificial pupil. Figure 1 shows a scheme of this device.

The micro-display subtended a visual angle of 114 x 86 arcmin with a resolution of 800 x 600 pixels (pixel size=0.143 arcmin). The luminance conditions of the experiment were manually adjustable. Aberrations up to the 5th order were dynamically compensated using a closed-loop system working at 1 Hz. This device comprised a double-pass of light through the eye, and then the total (eye-device) aberration encountered along the line of sight was measured. Moreover, this device was programmed to minimized the changes in ocular aberrations due to changes in accommodation, tear film, etc. Consequently, the most accurate retinal images of the visual performance tests were provided by these dynamically adjusting wavefronts, which enabled the compensation of small eye decentration and aberration variations due to the tear film or accommodation.
The AO systems required precise alignment of the individual’s pupil with the optical axis to the set-up (with the wavefront sensor and the deformable mirror). The pupil position was monitored using a charge-coupled device camera. The control hand wheel of the crx1 system enabled the pupil position to be maintained, providing a quick, smooth, and fine adjustment. To control the pupil size, this device has an artificial control pupil size to achieve the same pupil size at all measures. Moreover, decentrations caused by ocular movements were corrected by the pupil tracker system.

3.3. Zernike’s values

The Zernike’s values were extracted from Prakash et al. previous work\(^6\). In their study they determined the difference in HOAs between normal and idiopathic amblyopic eyes with a mean age of 9±3 years for a 6 mm pupil. To diagnose the idiopathic ambliopic eyes, they ruled out known causes of amblyopia and vision disparity. Their patients underwent dilated cycloplegic retinoscopy and subsequent refraction to evaluate the refractive error and anisometropia. Moreover, all patients, included in Prakash et al\(^6\) work, were screened for microtropia, tropia, cataract, ptosis, any macular or optic disc anomaly, optic nerve conduction deficit, visual field defects, previous history of any ocular or adnexal surgery and a documented history of higher magnitude of anisometropia in the past. They considered a poor compliance with amblyopia treatment protocols as an exclusion factor.

3.4. Experimental procedure

First, ocular aberrations of every subject were measured using a commercial aberrometer (irx-3, Imagine Eyes). Then, it was programmed to compensate ocular wavefront error up to the 5\(^{th}\) order and to simulate the aberration pattern of normal and amblyopic eyes, up to 4\(^{th}\) order. To carry out this procedure, the SVAO program was
used. After that, the crx1 was ready to start the measures of VA and CS. The procedure of measuring, compensating and simulating are summarized in figures 2-4.

Before starting the simulations, these values were escalated for 3- and 5.5-mm pupil sizes applying the formula developed by Schwiegerling\textsuperscript{7}. Table 1 shows the whole eye Zernike’s values of normal and amblyopic eyes for both pupil sizes.

<table>
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<th>Zernike’s coefficients</th>
<th>Normal 3mm</th>
<th>Normal 5.5mm</th>
<th>Amblyopia 3 mm</th>
<th>Amblyopia 5.5 mm</th>
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<td>z (3, -3) (µm)</td>
<td>0.0063</td>
<td>0.0385</td>
<td>0.0125</td>
<td>0.0770</td>
</tr>
<tr>
<td>z (3, -1) (µm)</td>
<td>-0.0213</td>
<td>-0.1309</td>
<td>-0.0213</td>
<td>-0.1309</td>
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<tr>
<td>z (3, 1) (µm)</td>
<td>0.0050</td>
<td>0.0308</td>
<td>0.0063</td>
<td>0.0385</td>
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<td>z (3, 3) (µm)</td>
<td>-0.0075</td>
<td>-0.0462</td>
<td>-0.0013</td>
<td>-0.0077</td>
</tr>
<tr>
<td>z (4, -4) (µm)</td>
<td>0.0006</td>
<td>0.0071</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>z (4, -2) (µm)</td>
<td>-0.0006</td>
<td>-0.0071</td>
<td>-0.0019</td>
<td>-0.0212</td>
</tr>
<tr>
<td>z (4, 0) (µm)</td>
<td>-0.0088</td>
<td>-0.0988</td>
<td>-0.0094</td>
<td>-0.1059</td>
</tr>
<tr>
<td>z (4, 2) (µm)</td>
<td>0.0037</td>
<td>0.0424</td>
<td>0.0006</td>
<td>0.0071</td>
</tr>
<tr>
<td>z (4, 4) (µm)</td>
<td>-0.0006</td>
<td>-0.0071</td>
<td>0.0025</td>
<td>0.0282</td>
</tr>
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Table 1. Zernike’s Values, expressed in µm, scaled for 3.00- and 5.50-mm pupil diameter.
Once the visual simulator was programmed, the subject started the VA and CS measurements. Each measurement was repeated 3 times. During this procedure no mydriatic or cyclopegic eye drops were instilled. Then, the room was darkened in order to achieve a natural pupil diameter up to 3- and 5.5-mm. To ensure that all measures were done for the same pupil diameter the artificial control pupil size was used.

3.5. Evaluation Optical Quality

To evaluate the optical quality of the eyes, the MTF and PSF of normal and amblyopic eyes were analysed. These metrics were computed using a custom-made MATLAB program (Mathworks, Inc., Nantick, MA) from the wavefront data reported by Prakash et al.\textsuperscript{6}.

3.6. Visual Quality Measurement

High (100%), medium (50%) and low (10%) contrast VA was measured using the Freiburg Visual Acuity Test (FrACT) software\textsuperscript{8} with a white background and luminance of 51 cd/m\textsuperscript{2}. The acuity threshold was determined by best parameter estimation following the sequential testing (PEST) procedure\textsuperscript{9} based on 30 presentations. It was an 8-alternative, forced-choice method. The individual task was identifying the Landolt-C gap position using a keypad. The VA value was retained as the average of 3 measurements. The VA measurement was taken for the normal and amblyopic eyes, and all measures were taken for 3- and 5.5-mm pupil diameters.

3.7. Contrast sensitivity measurement

The CS was measured for 3 spatial frequencies: 10, 20 and 25 cycles per degree (cpd). Oriented sinusoidal gratings (0°, 45°, 90° and 135°) were randomly generated and displayed on the micro-display using a 4-alternative, forced-choice method. A modified best PEST method based on 30 presentations was used to determine contrast thresholds. The sine-wave gratings were truncated by a windowing function, which consisted of a circular window subtending a visual angle of 1°. This window is surrounded by a
sinusoidal function subtending a visual angle of 0.14° to smooth the edge of the field. The presentation time of each grating was 500 ms. The individual was asked to indicate the grating orientation by pressing the appropriate button on a numeral keypad. At each frequency, 3 CS measurements were performed and the average was retained. The CS measurement was determined for normal and amblyopic eyes, and all measures were taken for 3 and 5.5 mm pupil sizes.

3.8. Data Analysis

A Student t-test for unpaired data was used for the comparison between normal and amblyopic eyes regarding VA and CS. Statistical significance of differences was considered when $P < 0.01$. 
4. Results

4.1. Optical quality

Figure 5 shows the MTFs of normal and amblyopic eyes for 3 and 5.5 mm pupils. For comparison purposes, the MTFs of the diffraction-limited (black line) and the retinal contrast threshold curve, which was found by Sekiguchi et al.\textsuperscript{10} at a retinal illuminance of 500 td, were also included.

For a 3 mm pupil size, the MTFs of normal (blue dashed-line) and amblyopic eyes (red dotted-line) were close to diffraction-limited. However, for a large pupil diameter (5.5 mm) both MTFs worsened moving away from the diffraction-limited curve. Moreover, for a 5.5 mm pupil, the MTF of amblyopic eyes (red line) was slightly lower than that obtained for normal eyes (blue line). The Sekiguchi’s et al.\textsuperscript{10} curve suggest that for amblyopic and normal eyes, with a 3 mm pupil, spatial frequencies up to about 50 cpd should be recognizable, corresponding to about 20/12 (visual resolution in white light). Note that the cut-off frequency for both ocular results, come from the intersection between the MTF of the normal and amblyopic eye and the neural curve. For a 5.5 mm pupil, the cut-off frequencies for the normal and amblyopic eyes were similar, about 35 cpd, corresponding to about 20/16. Note that, because of the retinal threshold curve rises steeply at higher frequencies, normal and amblyopic eyes do not greatly increase the cut-off frequency. However, the retinal contrast threshold does not increase the supra-threshold contrast at lower spatial frequencies.
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Figure 6 shows the PSFs of normal and amblyopic eyes for 3 and 5.5 mm pupils. PSFs were similar for a 3 mm pupil (two top figures). However, these images worsened when the pupil diameter increased to 5.5 mm for both groups (two bottom figures).
4.2. Visual acuity

Figure 7 shows the VA results for 100%, 50% and 10% contrast levels after inducing the aberration patterns of normal and amblyopic eyes for a 3 mm pupil size. LogMAR VA results, obtained for a 100% contrast, were good for normal and amblyopic patterns, about -0.11±0.05 and -0.06±0.04 respectively (>20/20). For a 50% contrast level, VA results were about -0.06±0.06 for normal pattern and 0.00±0.05 for amblyopic one. For a 10% contrast level, VA results for normal pattern were 0.17±0.07 and 0.21±0.06 for amblyopic one (about 20/32). No statistically significant differences were found in VA between both groups at any contrast studied (P>0.01).

![Log contrast sensitivity for normal and amblyopic patterns for a 3 mm pupil at different spatial frequencies (cycles per degree).](image)

Figure 7.

Figure 8 shows the VA results obtained for 100%, 50% and 10% contrast levels for normal and amblyopic patterns at 5.5 mm pupil. The logMAR VA outcomes, at 100% contrast level, were similar for both groups (about 0.00±0.04, 20/20). At 50% VA results were about 0.10±0.10 for both normal and amblyopic patterns. For the lowest contrast level VA results were about 0.35±0.09 for both groups (about 20/40). As previously at 3 mm pupil diameter, no statistically significant differences were found in VA between both groups at any contrast studied (P>0.01).
4.3. Contrast sensitivity

Figure 9 displays the CS results obtained at 3 mm pupil for normal and amblyopic patterns. At 10 cpd, log CS values for normal and amblyopic patterns were 1.9±0.2 and 1.7±0.1, respectively; at 20 cpd these values changed to 1.2±0.15 and 1.1±0.2 and at 25 cpd to 0.9±0.1 and 0.8±0.2, respectively. No statistically significant differences were found in CS between both groups at any spatial frequency studied (P>0.01).
With regards to the CS results obtained for a 5.5 mm pupil, these are displayed in figure 10. Results were similar between both groups for 10, 20 and 25 cpd, yielding logCS values of 1.4±0.1, 0.9±0.2, and 0.6±0.1, respectively. No statistically significant differences were found (P>0.01).

**Figure 10.** Log contrast sensitivity (CS) for normal and amblyopic patterns for a 5.5 mm pupil at different spatial frequencies. X-label displays the spatial frequency in cycles per degree. Y-label displays the log CS.
5. DISCUSSION

The aim of the present study was to evaluate the effect of HOAs, related to idiopathic amblyopic eyes, on the visual performance. Consequently, it could be elucidated if amblyopic HOAs pattern affect the visual performance and if it has any possible role in the development of the condition, as previously suggested by some authors\textsuperscript{5,6,13}. To comparison purposes, optical quality and visual performance results were compared with those resulting from normal eyes HOAs. The methodology implied visual simulation inducing specific patterns from amblyopic and normal eyes in a sample of subjects in which their own aberrations were previously compensated by adaptive optics. The method allows the assessment of visual performance in the same patient when the two aberration patterns were sequentially simulated, first a normal eye and then an amblyopic eye aberration pattern.

The MTF shows how an optical system transmits spatial frequencies. In this function curve there is a cut-off frequency value after which no spatial frequency is transmitted. The loss of high frequencies means a loss of information regarding the details of an object, decreasing image quality and hence VA. For a 3 mm pupil size (figure 5), both groups showed good MTFs close to the diffraction-limited curve. These outcomes were correlated to the small PSFs reported (figure 6). However, when the pupil diameter increased to 5.5 mm, the MTFs (figure 5) after inducing both normal and amblyopic patterns worsened, moving away from the diffraction-limited reference. These outcomes also correlated with worse PSFs (figure 6). Poor MTF and PSF for large pupil diameter are related with the increase of aberrations at larger pupils\textsuperscript{11,12}.

With regards to VA and CS values (figures 7-10), no statistical significant differences were found between normal and amblyopic eyes for any pupil size, contrast level or spatial frequency (P>0.01). These results agree with the optical quality metrics analysed (MTFs and PSFs) being also very similar between both groups. Thus, it does
not seem likely that HOAs have a main role in compromising visual performance of idiopathic amblyopic eye and therefore, have not a role in its onset. Prakash et al. did not found statistical significant differences between normal and amblyopic HOAs. However, they applied a steep wise regression and they found differences in HOA patterns between normal and amblyopic eyes. Their results provide evidence towards a difference in wavefront regression patterns, especially of third order aberrations, in some patients of amblyopia previously labelled as ‘idiopathic’. However, the results obtained in this study reveal that these differences in HOAs patterns are not noticed perceptually.

Some authors suggested that HOAs might play a role as an amblyopiogenic factor. They suggested that differences in HOAs between two eyes could be a possible risk factor leading to disturbing bifoveal fusion, important during the sensitive period of developing stereopsis. Peng-fei et al. studied the wavefront aberration in 262 amblyopic children’s eyes and analysed the mechanism of the wavefront aberration in the formation of the amblyopia. They found that whole root-mean-square (RMS), 5th order aberrations, defocus (Z_2^0), astigmatism (especially Z_2^2) and vertical coma (Z_3^{-1}) were higher in amblyopic groups than in normal eyes group. These authors commented that precisely focused images are required during the entire period of visual development; and a dose-response relationship exist between the reduction in the quality of retinal images and the severity of amblyopia, which is also associated with age. However, the results obtained in this study reveal that, apparently, differences in HOAs patterns between both eyes are not a risk factor to develop amblyopia because visual function obtained after simulation of normal and amblyopic HOAs were similar because of no statistical significant differences (P>0.01) were found. Then it means that the principal risk factor to develop amblyopia is the lower order aberrations (defocus and astigmatism) as was proposed by Peng Fei et al. and Liang et al. These authors
found that lower order aberrations such as defocus (myopia and hyperopia) and astigmatism are responsible for about 90% of the quality of the retinal image. The remaining 10% is a combination of the effects of the HOAs such as coma, spherical aberration and trefoil.

Kwan et al\textsuperscript{15} reported that coma and spherical aberration are the most common elements among the HOAs in normal subjects. A study of Wei et al\textsuperscript{16} about children eye aberrations, showed that the 3\textsuperscript{rd} order aberrations were the main aberrations and that vertical coma ($Z_{3}^{-1}$) accounted for the greatest percentage in the three main aberrations in HOAs namely coma ($Z_{3}^{-1}$ and $Z_{3}^{1}$) and trefoil ($Z_{3}^{3}$ and $Z_{3}^{3}$) in 3\textsuperscript{rd} order aberrations, and spherical aberration ($Z_{4}^{0}$) in 4\textsuperscript{th} order aberration, in a Chinese population. The Zernike’s coefficients used in this study to simulate the pattern aberrations are in agreement with Kwan et al\textsuperscript{15} and Wei et al\textsuperscript{16}: 3\textsuperscript{rd} order coma accounted for the greatest percentage in the three main aberrations in HOAs namely coma ($Z_{3}^{-1}$ and $Z_{3}^{1}$) and trefoil ($Z_{3}^{3}$ and $Z_{3}^{3}$) in 3\textsuperscript{rd} order aberrations, and spherical aberration ($Z_{4}^{0}$) in 4\textsuperscript{th} order aberration. On the other hand, Applegate et al\textsuperscript{17} argued that the aberration was greater near the central line of the Zernike polynomials and thus deduced that defocus reduced vision more easily in lower order aberrations and that coma had a greater effect on vision in HOAs. This argument was used by Peng-fei et al\textsuperscript{13} to suggest that coma (specially vertical coma) of the HOAs might influence the development of vision to some extent in children with amblyopia. However, I elucidated that, apparently, coma vertical might not affect the visual function because the VA and CS results obtained were good and comparable as results obtained with normal eyes.

The present study points out similar visual outcomes between normal and amblyopic eyes when HOAs were simulated. The results obtained reveal that there were not statistical significant differences ($P>0.01$) in the visual performance between both types of eyes. This is because Zernike values, which were used for the visual
simulation, were similar and hence visual performance is expected to be similar too. The HOA RMS values for normal and amblyopic eyes were 0.17 \( \mu \m \) and 0.19 \( \mu \m \), respectively (at 5.5 mm pupil). This agrees with those found by Peng-fei et al\(^{13} \), who reported HOA RMS values (at 6 mm pupil) for different eyes of: 0.28\( \pm \)0.12 \( \mu \m \) for a normal eyes group (refractive error between -0.25 and +0.50D); 0.27\( \pm \)0.14 \( \mu \m \) for corrected amblyopic eyes (best corrected vision \( \geq \)0.9 Snellen decimal); 0.30\( \pm \)0.12 \( \mu \m \) for amblyopic group; and 0.32\( \pm \)0.17 \( \mu \m \) for refractory amblyopic group (in which the best corrected vision maintained was 0.7-0.8 Snellen decimal). They did not find statistical significant differences between these ocular conditions. This reveals that apparently, the differences in HOAs are not a risk factor to develop an amblyopia because of the RMS which Peng-Fei et al\(^{13} \) report are similar. This supports the hypothesis that the main risk factor to develop an amblyopia is differences in low order aberrations and not in HOAs. However, more studies are need to confirm this hypothesis.

Actually, Carkeet et al\(^{18} \) measured the monochromatic aberrations in Singaporean children. The subjects were grouped in high myopes (refractive error \( \leq \) -3D), low myops (\(-3 \leq \) refractive error \( \leq \) -0.5D), hyperops (refractive error \( \geq \) +1D) and emmetrops (\(-0.5 \leq \) refractive error \( \leq \) +1D). The percentages of the HOAs RMS values were about 8% for low myopia, 6% for hyperopia, 4% for high myopia and 4% for emmetropia (at 6 mm pupil). This shows that the HOAs percentage is lower than lower order aberrations, then, it is expected that the role of HOAs in amblyopia development should be minimal, being low order aberrations the critical component. This agrees with the outcomes, which have been reported in this study, since no differences in visual performance were found between normal and amblyopic eyes. VA results agree with cut-off frequency obtained in figure 2 considering the optical quality simulated. For a 3 mm pupil, the VA predicted was about 20/12, and experimental results, for normal and
amblyopic eyes, were about 20/16. For a 5.5 mm pupil, the VA predicted was about 20/20, and the experimental results for normal and amblyopic eyes were about 20/20. This supports the outcomes found in the VA and CS experimental study.

Prakash et al\textsuperscript{11} studied the HOAs in idiopathic amblyopic children, as a possible cause. They considered that resolved anisometropia with residual amblyopia might be a possible explanation for idiopathic amblyopia. They considered, that if children had a residual amblyopia with resolving anisometropia, the stimulus that caused amblyopia (i.e. anisometropia) was not present any more, and they might have shown a response to patching protocols. But if they do not response to it, this would have been because the amblyopiogenic factor would have been still uncorrected. Then, they hypothesized that if the difference in HOA patterns between the two eyes in case of idiopathic amblyopia could have present since early childhood, it could have led to a bifoveal pattern disruption resulting into HOA associated amblyopia. Finally, they concluded that it seems a strong possibility that a subset of idiopathic amblyopia may be associated with the loss of symmetry in wavefront patterns of the two eyes.

However, other differences between normal and amblyopic eyes should be carefully analysed to find causes for amblyopia development. For example, Park et al\textsuperscript{19} compared, in a pilot study, the thickness of each retinal layer of amblyopic and fellow eyes in patients with unilateral amblyopia. They found that in amblyopic eyes there was significant thinning of the ganglion cell layer plus inner plexiform layer at all four nasal and temporal macular locations and at the outer superior and inferior locations. The other retinal layers, including the nerve fibre layer, inner nuclear layer, outer plexiform layer and outer nuclear layer, demonstrated significant differences in thickness at several macular locations. They indicated that visual cortex has been strongly suggested as a primary site of amblyopia\textsuperscript{20,21}. However, Park et al\textsuperscript{19} cannot exclude the possibility that altered visual stimuli in amblyopic eyes directly affect functions and structures of
some retinal cells. Some authors of previous animal studies suggested that a lack of visual stimuli can affect particular retinal cells that carry out the processing of visual information\textsuperscript{22,23}. They hope that further prospective studies, with larger sample sizes, may reveal more clearly abnormalities in retinal microstructures and their clinical significance in patients with amblyopia.

Finally, it can be concluded that although some authors had found differences in HOAs patterns between normal and amblyopic eyes, the results obtained reveal that this differences are not noticed perceptually because differences in VA and CS were not found between normal and amblyopic eyes. This confirms that HOAs alone do not affect the visual function of idiopathic amblyopic eyes and its relationship with the development of amblyopia. However, it should be considered some limitation of the present study: the sample used was relatively small; pattern aberrations were taken from children and these were simulated in adults and for a specific study. Further studies increasing the sample of subjects, evaluation of children and different wavefront patterns should be done to fully analyse the role of HOAs with amblyopia.
5. DISCUSSION

El objetivo de este estudio fue estudiar el efecto de las HOAs de ojos ambliopes en la función visual. De esta forma se podrá elucidar si estas afectan a la función visual y si son un posible factor de riesgo para desarrollarla, tal y como ha sido propuesto anteriormente por algunos autores\textsuperscript{5,6,13}. Para hacer comparaciones, los resultados de la calidad óptica y la función visual se compararon con los obtenidos al utilizar HOAs de ojos normales. La metodología utilizada implica la simulación visual de distintos patrones aberrométricos específicos, ojos normales y ambliopes, en una muestra de sujetos a los que previamente se les habían compensado sus aberraciones utilizando la óptica adaptativa. Con este método se puede evaluar la función visual, en un mismo paciente, cuando se le inducen dos patrones aberrométricos distintos, primero el correspondiente a ojos normales y el segundo a ojos ambliopes.

La MTF representa cómo se transmiten las frecuencias espaciales a través de un sistema óptico. En esta curva hay una frecuencia de corte a partir de la que no se transmiten frecuencias espaciales más altas. La pérdida de altas frecuencias espaciales implica la pérdida de información de los detalles de un objeto, disminuyendo la calidad del mismo y por tanto la AV. Los dos grupos estudiados muestran buenas MTFs, próximas a la curva del límite de difracción, para 3 mm de diámetro pupilar (figura 5). Estos resultados se correlacionan con el tamaño de las respectivas PSFs (figura 6). Sin embargo, cuando el diámetro pupilar aumentó hasta los 5,5 mm, las MTFs (figura 5) empeoran alejándose de la curva del límite de difracción, tanto la de los ojos ambliopes como la de los normales. Estos resultados también se correlacionan con un empeoramiento de las PSFs (figura 6). Una MTF y PFS de baja calidad para grandes diámetros pupilares se correlaciona con un aumento en las aberraciones oculares en tamaños pupilares grandes\textsuperscript{11,12}. 
En cuanto a los valores de AV y SC (figuras 7-10), no se encontraron diferencias estadísticamente significativas (P>0,01) entre los ojos normales y ambliopes para ningún diámetro pupilar, nivel de contraste o frecuencia espacial. Estos resultados se corresponden con las métricas de calidad óptica analizadas (MTF y PSF), siendo muy similares entre ambos grupos. Por todo ello, se puede decir que solo las HOAs no afectan a la función visual de pacientes diagnosticados de ambliopía idiopática. Además, Prakash et al\(^6\) no encontraron diferencias estadísticamente significativas entre los valores medios de cada coeficiente de Zernike de alto orden entre los ojos normales y ambliopes. Sin embargo, aplicaron una regresión paso a paso y encontraron que los patrones aberrométricos de los ojos normales y ambliopes eran diferentes. Siendo estas diferencias mayores en el tercer orden. Sin embargo, los resultados obtenidos en este estudio revelan que estas diferencias en los patrones aberrométricos no se notan perceptualmente.

Algunos autores\(^5,6\) sugieren que las HOAs podrían ser un factor de riesgo a la hora de desarrollar una ambliopía. Estos sugieren que diferencias en las HOAs entre los dos ojos puede ser un posible factor de riesgo porque podría afectar a la fusión bifoveal, importante durante el desarrollo de la estereopsis. Peng-fei et al\(^13\) estudió las aberraciones en 262 niños ambliopes y analizó los coeficientes que pueden ser considerados como un factor ambliogénico. Encontraron que el error cuadrático medio (RMS) total, las aberraciones de 5° orden, el desenfoque (XX), el astigmatismo (especialmente el ZXX) y el coma vertical (XX) fueron mayores en el grupo de ojos ambliopes que en el de ojos normales. Estos mismos autores destacaron que se necesita una imagen perfectamente enfocada en la retina durante el periodo del desarrollo visual; y que existe una relación muy fuerte entre la reducción de la calidad en imagen retiniana y la severidad de la ambliopía, que también está asociada con la edad\(^4,13\). Sin embargo, los resultados obtenidos en este estudio revelan que, aparentemente, las diferencias en
los patrones de HOAs entre ambos ojos no son un factor de riesgo para desarrollar una ambliopía, porque la función visual obtenida tras la simulación de patrones de alto orden referentes a ojos normales y ambliopes fueron similares, ya que no se encontraron diferencias estadísticamente significativas (P>0,01). Como consecuencia, se puede deducir que el principal factor de riesgo para desarrollar una ambliopía son las aberraciones de bajo orden (astigmatismo y desenfoque), tal y como fue propuesto por Peng Fei et al\textsuperscript{13} y Liang et al\textsuperscript{14}. Estos autores encontraron que las aberraciones de bajo orden, como el desenfoque (miopía e hipermetropía) y el astigmatismo son responsables del 90% de la calidad de la imagen retiniana. El 10% restante es una combinación de los efectos de las HOAs, como por ejemplo, el coma, la aberración esférica y el trifoil.

Kwan et al\textsuperscript{15} concluyeron que el coma y la aberración esférica eran las aberraciones más comunes entre las HOAs de los ojos normales. Un estudio de Wei et al\textsuperscript{16} donde estudiaban las aberraciones en niños, encontraron que las aberraciones de 3\textsuperscript{a} orden son las aberraciones más altas, y de entre estas, el coma vertical (ZXX) obtuvo el mayor porcentaje. Los coeficientes de Zernike utilizados en este estudio para hacer las simulaciones no contradicen los resultados de Kwan et al\textsuperscript{15} y Wei et al\textsuperscript{16}: El coma de 3\textsuperscript{a} orden es el coeficiente que tiene un mayor porcentaje entre las HOAs. Por otro lado, Applegate et al\textsuperscript{17} argumentaron que las aberraciones con valores más grandes estaban próximas a la línea central de la pirámide de polinomios de Zernike. De aquí dedujeron que el desenfoque afecta más a la visión en las aberraciones de alto orden, y el coma afecta más en las HOAs. Este argumento fue utilizado por Peng-Fei et al\textsuperscript{13} para sugerir que el coma (especialmente el coma vertical) de entre las HOAs podría influir en el desarrollo visual de algunos niños, dando como resultado una ambliopía. Sin embargo, con los resultados obtenidos en este estudio, se puede decir que aparentemente, el coma vertical no afecta a la función visual porque los valores de AV y SC obtenidos, al
simular el patrón de HOAs de ojos ambliopes, eran buenos y comparables con los obtenidos al simular los ojos normales.

El presente estudio refleja que no existen diferencias estadísticamente significativas (P>0,01) entre los resultados obtenidos al simular el patrón aberrométrico correspondiente a ojos normales y ambliopes. Un posible explicación se encuentra en que los coeficientes de Zernike que se han utilizado para llevar a cabo las simulaciones son muy similares, y por tanto, era de esperar que los resultados visuales fuesen también similares. El RMS de las HOAs para ojos normales y ambliopes fue de 0,17 µm y 0,19 µm, respectivamente (para 5,5 mm de diámetro pupilar). Estos valores son favorables a los obtenidos por Peng-fei et al\textsuperscript{13}, quienes reportaron los valores del RMS de alto orden (considerando 6 mm de diámetro pupilar) para distintas condiciones oculares: 0.28±0.12 µm para el grupo de ojos normales (error refractivo entre -0.25 y +0.50D); 0.27±0.14 µm para ojos ambliopes corregidos (mejor agudeza visual ≥0.9, en escala decimal); 0.30±0.12 µm para el grupo ambloipe; and 0.32±0.17 µm para el grupo de ambliopía refractiva (en el que la mejor AV fue 0.7-0.8, en escala decimal). Además, estos autores no encontraron diferencias estadísticamente entre los grupos estudiados. Esto es otro signo de que aparentemente, las diferencias en las HOAs no son un factor de riesgo para desarrollar una ambliopía porque en los RMS que aportan Peng-Fei et al\textsuperscript{13} son similares. Todo esto viene a apoyar la hipótesis que el principal factor de riesgo para desarrollar una ambliopía son diferencias en las aberraciones de bajo orden y no en las de alto orden. Sin embargo, se necesitan más estudios para poder afirmar esta hipótesis.

De hecho, Carkeet et al\textsuperscript{18} midieron las aberraciones monocromáticas en niños de Singapur. Estos fueron agrupados in miopes elevados (error refractivo ≤-3D), miopes bajos (-3D ≤ refractive error ≤ -0.5D), hipermétropes (refractive error ≥+1D) y emétropes (-0.5D ≤ refractive error ≤+1D). El porcentaje de HOAs respecto al RMS
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total fue del 8% para miopías bajas, 6% para hipermetropías, 4% para miopías elevadas y 4% para emétropes (considerando 6 mm de diámetro pupilar). Esto muestra que el porcentaje de las HOAs es menor en comparación con las de bajo orden. Por tanto, es de esperar que el rol de las HOAs en el desarrollo de la ambliopía sea muy pequeño, siendo las aberraciones de bajo orden el factor fundamental. Esto está de acuerdo con los resultados que se han obtenido en este estudio, porque no se han encontrado diferencias en la función visual entre los ojos normales y ambliopes. Además, los valores de AV que predice la MTF, para 3 mm de pupila, es del orden de 20/12 para los dos grupos, y los resultados experimentales son 20/16. Para 5,5 mm, la AV predicha es del orden de 20/20, y los resultados experimentales obtenidos para los dos grupos son 20/20. Esto viene a reforzar los resultados experimentales obtenidos en la AV y SC.

Prakash et al\textsuperscript{11} estudiaron las HOAs como posible causa de ambliopía idiopática. Sin embargo, consideraron que una anisomeropía resuelta durante la infancia puede dar como resultado una ambliopía residual y que además puede explicar la ambliopía idiopática. Estos autores consideraron, que si un niño tiene una ambliopía como consecuencia de una anisometropía, que se resuelve durante la infancia, el estímulo que causa la ambliopía ya no está presente, y estos podrían responder adecuadamente a los protocolos de oclusión. Sin embargo, si no responden a los protocolos puede ser porque el factor ambliogénico sigue estando presente. Por tanto, estos autores hipotetizaron que si la diferencia en las HOAs entre los dos ojos está presente desde el nacimiento, puede dar como resultado una afectación de la imagen bifoveal, causando una ambliopía asociada a las aberraciones de alto orden. Finalmente, estos autores concluyeron que hay una probabilidad muy grande de que haya casos de ambliopía idiopática asociada a la pérdida de simetría en el frente de onda entre los dos ojos.
Sin embargo, otras diferencias entre el ojo normal y ambliope deberían analizarse para encontrar causas de posibles desarrollos de ambliopía. Por ejemplo, Park et al\textsuperscript{19} compararon, en un estudio piloto, el espesor de cada capa de la retina de ojos ambliopes con sus contralaterales, en pacientes con ambliopía unilateral. Los resultados obtenidos demostraron que en los ojos ambliopes había un adelgazamiento significativo de la capa de células ganglionares, capa plexiforme interna, capa de fibras nerviosas, capa nuclear interna, capa plexiforme externa y la capa nuclear externa. Además, estos autores indicaron que el córtex visual ha sido considerado como la zona principal que se va a ver afectada en los casos de ambliopía\textsuperscript{20,21}. Sin embargo, Park et al\textsuperscript{19} no pueden excluir la posibilidad que sean los estímulos visuales quienes afecten directamente la función y estructuras de las distintas capas de la retina, causando una ambliopía. Algunos autores con estudios llevados a cabo con animales sugieren que la falta de estímulo visual puede afectar a algunas células de la retina que se encargan del procesado de la información visual\textsuperscript{22,23}. Sin embargo, Park et al\textsuperscript{19} consideran que se necesitan más estudios prospectivos, con una muestra poblacional más grande, para poder revelar con mayor claridad anormalidades en microestructuras de la retina y su significancia clínica en pacientes con ambliopía.

Finalmente, se puede concluir que algunos autores han encontrado diferencias en los patrones de HOAs entre los ojos normales y ambliopes. Sin embargo, los resultados experimentales revelan que estas diferencias no se perciben perceptualmente ya que no se encontraron diferencias (P>0,01) en los valores de AV y SC entre los ojos normales y ambliopes. Esto confirma que solo las HOAs no afectan a la función visual de ambliopías idiopáticas ni al desarrollo de tal condición ocular. Sin embargo, deben considerarse algunas limitaciones en el estudio: el tamaño de la muestra es pequeño; los patrones aberrométricos se han obtenido en niños y se han simulado en adultos para un estudio específico. Sin embargo, sería interesante poder hacer más estudios aumentando
el tamaño de la muestra, hacer las simulaciones en niños y considerar diferentes patrones de HOAs para analizar el efecto que tienen las HOAs en la ambliopía.
6. References


