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Evaluating the effect of ocular aberrations on the simulated performance of a new refractive IOL design using adaptive optics

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Abstract: Adaptive optics (AO) visual simulators are excellent platforms for non-invasive simulation visual performance with new intraocular lens (IOL) designs, in combination with a subject own ocular aberrations and brain. We measured the through focus visual acuity in subjects through a new refractive IOL physically inserted in a cuvette and projected onto the eye's pupil, while aberrations were manipulated (corrected, or positive/negative spherical aberration added) using a deformable mirror (DM) in a custom-developed AO simulator. The IOL increased depth-of-focus (DOF) to 1.53 ± 0.21D, while maintaining high Visual Acuity (VA, -0.07 ± 0.05), averaged across subjects and conditions. Modifying the aberrations did not alter IOL performance on average.

1. Introduction

The seminal publication by Liang et al on an AO for eye research demonstrated both improved resolution in retinal imaging and a benefit of correcting aberrations on visual performance [1]. Over the years, numerous applications have been developed aiming at understanding the optical limits to spatial vision, the effect of aberrations on accommodation, neural adaptation to aberrations, or the impact of different optical corrections (i.e. multifocal contact lenses or intraocular lenses) on vision. Several review papers describe some of those applications [2,3].

One of the most sought applications of AO visual simulators is the simulation of visual performance with intraocular lenses [4,5]. In an IOL design development stage, experimental visual simulation of the IOLs in human subjects allows non-invasive testing of the lens design in combination with the optics of the cornea and neural visual processing, an important step beyond computer eye modeling and on bench testing. Visual simulators contain active elements (normally a Spatial Light Modulator (SLM) or a DM) conjugated to the pupil plane where a phase map representing the IOL is mapped. Most of AO visual simulators are laboratory prototypes, although some commercial devices are available, including VAO by Voptica [6] based on SLM. In addition, there are commercial visual simulators not based on AO such as SimVis by 2EyesVision [7] that operates under the principle of temporal multiplexing [8].

Several studies have used AO Visual Simulators to investigate the impact of inducing spherical aberration (SA) on visual performance, on accommodation and on the eye's depth-of-focus in normal eyes. On the other hand, as new IOL designs are deployed, many of them aiming at providing multiple focus or expanding depth-of-focus to improve vision functionality at near and intermediate distances in subjects that do not have the capability to accommodate, a question that arises is to what extent the optical performance and the nominal functionality of these IOLs

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(i.e. depth-of-focus) is affected by the magnitude of corneal aberrations, and preserved upon differences in the underlying spherical aberration.

In previous works we have shown the accuracy of the representation of diffractive and segmented lenses by a SLM or by temporal multiplexing (SimVis) by comparing the through-focus visual acuity in subjects with the simulated IOLs pre-operatively, and post-operatively with the corresponding implanted IOL [9,10]. In other works comparisons were performed on the same phakic subjects with phase-plates [11] or IOLs inserted in a cuvette [4] projected onto the subject's eye and the simulated IOL (generally on a SLM). In a recent publication, we presented a modification of the Rassow lens-based system to eliminate the IOL base power without altering magnification [12]. In these studies, we found a good correspondence between the subject's visual performance with the SLM-represented IOL and the physical IOL in the cuvette, in tests performed with monofocal, diffractive trifocal and refractive extended depth of focus IOLs (Podeye IOL, FineVision and Isopure IOL by BVI-PhysIOL)

In this study we further investigated the interaction of eye's aberrations and the Isopure IOL, a bi-aspheric refractive design with aspheric coefficients up to the 10th order in each surface. The IOL has been designed using a multiconfiguration approach, optimizing a retinal image quality metric (spread of spots in the retinal spot diagram) both at best focus and intermediate distances, while keeping performance relatively independent of the pupil size [13]. The optimization was individually performed for each IOL power, on computer eye models with variable axial lengths. The IOL was immersed in a cuvette in one of the channels of the AO Visual Simulator and projected onto the subject's pupil while different amounts of spherical aberration were introduced in the DM of the visual simulator.

2. Methods

2.1. AO system

Measurements have been undertaken using a custom developed AO Visual Simulator that has been described in detail in previous publications by our group [11,12]. The following channels have been used in the current study: (1) Illumination channel with a Super Continuum Laser Source (SCLS) with selectable emission wavelength; (2) Hartmann-Shack wavefront sensor; (3) 52 actuators DM, which we used in the current study to compensate for the aberrations of the optical system and to induce spherical aberration; (4) Badal system to induce defocus; (5) Digital Micromirror Device (DMD) to present a visual stimulus, illuminated with the supercontinuum laser source (555 nm) through a holographic filter (6) Double-pass retinal imaging capture, to register the images of a circular object (6 arcmin) projected onto the retina and imaged back onto a CCD camera (ORCA-R2, Digital CCD camera, C10600-10B, Hamamatsu Photonics K.K., Japan, 12 or 16 bit, 1344×1024 pixels, 6.45×6.45µm pixel size) ; (7) Cuvette channel allowing to project a physical IOL with power ranging from 15 to 25 D onto the subject´s pupil, compensating the IOL optical power.

2.2. Intraocular lens and cuvette

All measurements were performed with an Isopure IOL (PhysIOL-BVI, 21D), a refractive, hydrophobic, with smooth aspheric surfaces (described by the radius of curvature and with aspheric coefficients up to the 10th order in each surface). This IOL, referred as enhanced monofocal IOL, was designed to allow vision at far and intermediate distances with optimal vision at far [13,14], and has been shown to extended depth of focus (EDOF) over the standard monofocal IOL (Micropure) [12,15,16].

The cuvette has a metallic support where the IOL is mounted and immersed in distilled water to simulate ocular media. The Rassow lens was placed at an optical distance twice it's focal length (120-mm) from the IOL plane and was designed to compensate a 20 D IOL power and to

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conjugate it with the entrance pupil plane of the eye. In this study the Isopure IOL power is 21 D and the Badal optometer was combined with the Rassow system to compensate the IOL residual defocus of 1 D. An Isopure IOL was projected on the entrance pupil of an artificial eye (on bench measurements) and on the subject's eye pupil.

2.3. DM spherical aberration mapping

The DM was configured to correct the aberrations of the system and to study the IOL performance with and without natural aberrations and with additional spherical aberration Vision was studied in four configurations: (1) Natural aberrations with the IOL projected onto the subject eye; (2) correcting natural aberrations with the DM, i.e. mimicking an ideal condition of "implanting" the IOL in an aberration free eye, (3) inducing positive SA with the DM (+0.2µm, 4.5-mm pupil diameter) on top of the subject's natural aberrations, (4) inducing negative SA (−0.2µm, 4.5-mm pupil diameter) on top of the subject's natural aberrations. These spherical aberrations are equivalent to inducing 0.87 µm over a 6.5-mm pupil diameter using scaling formulas derived by Schwiegerling et al [17], close to previously reported values of spherical aberration induced by a 5 D myopic corneal refractive surgery a couple of decades ago [18,19]. As a control condition, the same procedures were followed, with no IOL, bypassing the cuvette.

2.4. On bench measurements

An artificial eye, mounted in place of the subject's eye (in a 3-D translational stage), was used to evaluate the optical performance of the combination of the IOL and spherical aberration on bench. The artificial eye consisted of a 50-mm focal length achromatic doublet with either a rotating diffuser as retina for the retinal image quality measurements (for double pass retinal image quality measurements) or a CCD camera (DCC1240C - High-Sensitivity USB 2.0 CMOS Camera, 1280 × 1024, Global Shutter, Color Sensor; Thorlabs GmbH, Munich, Germany) where images of visual stimuli were projected.

Single pass (1P), through focus retinal image quality was studied with the CCD camera of the eye model. A Snellen E letter was displayed in the DMD (letter size 45 pixels, 0.15 degrees angular subtend, equivalent to a VA of 0.3 LogMAR) with black background and projected onto the retina, i.e. the CCD camera. Series of images were collected through focus in a range between -4.0 to +1.0 D, in steps of 0.25 D changing the vergence with the Badal system.

Through-focus double-pass retinal images (2P) were collected illuminating the eye with a collimated beam changing the vergence of the rays with the Badal system between -3.0 and +1.0 D, in steps of 0.25 D. All measurements were performed at 4.5-mm pupil diameter, wavelength illuminating the stimulus was 555 nm light, with constant laser power and camera properties, and ensuring that none of the images were not saturated.

2.5. Subjects

The study was performed on ten 10 young subjects (9 female, 1 male), with an average age of 29.8 ± 3.4 years, and average spherical error of -0.17 ± 1.10 D. Astigmatism was less than 0.75 D in all subjects. Measurements were obtained under cycloplegia (tropicamide 1%). The study protocols were approved by CSIC Institutional Review Boards. Subjects consented after they had been informed on the nature of the study, protocols and implications of their participation.

2.6. Measurement protocols in subjects

Subjects viewed the psychophysical stimuli projected on the DMD, illuminated at 555 nm, and viewed through the real IOL immersed in the cuvette and a DM simulating different amounts of spherical aberration. The subject's eye pupil center was aligned with the optical axis of the system with an x-y-z stage and stabilized with a dental impression on a bite bar and monitored with the pupil camera. As a second step, the subjects selected their best focus (repeated 3 times)

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by moving the mirrors Badal optometer with a numerical keyboard while looking at a Maltese cross. The search for the best focus was initiated with 2 D of myopic defocus over their spherical refraction using a step size of 0.05 D. The search for best focus was repeated before each TF VA measurements with the conditions of the measurement (IOL projected and aberration correction state), since subject's best focus shifted with the induction of SA and when aberrations were corrected, or in the no IOL condition because of the residual IOL defocus (1D).

The test selected to measure the Visual Acuity (VA) was a tumbling E letter with 8-Alternative Forced Choice (8AFC). The orientation and size of the E letter was calculated according to the subject's response with a QUEST (Quick Estimation by Sequential Testing) algorithm [20–23]. Subjects indicated the orientation of the E letter (presented for 0.5 seconds) with a numerical keyboard. In this study 32 trials and 20 reversals were used for each VA measurement. The result was calculated as the mean of the last 10 reversals and the variability as the standard deviation of those 10 values. VA measurements were performed under cycloplegia. The data for this study were collected as part of larger study in three sessions that lasted 210 minutes.

2.7. Data analysis

For one-pass on bench measurements, the optical quality was measured in terms of the correlation metric, obtained as the correlation of the degraded E-letter image, i.e. the images taken through the Isopure IOL, with the E-letter obtained without an IOL in the system at best focus. For double-pass retinal images, the optical quality metric was the Full Width at Half-Maximum (FWHM) of the double-pass retinal images, calculated as the average FWHM of the intensity profile of four meridians passing through the center of the PSF. Optical degradation at far was defined as the optical quality at 0 D relative to the no IOL condition, and optical benefit at intermediate as the average optical quality in the (1.50 D range) to the no IOL condition. Using both the correlation metric and the normalized FWHM the DOF on bench was defined as the range of diopters above 0.8 [24].

In subjects, the impact of aberration correction and spherical aberration induction was assessed in terms DOF, which was estimated from the TF curves as the range the defocus range (in the near region, i.e. negative defocus) for which VA was 0.2 LogMAR or better [25]. Visual degradation at far was defined as the difference in VA LogMAR at 0 D relative to the no IOL condition, and optical benefit at intermediate as the average optical quality in the (1.25 D range) to the no IOL condition [26]

ANOVA was used to evaluate statistical differences across conditions.

3. Results

3.1. Experimental through-focus optical quality (on bench)

Through-focus (TF) optical quality was assessed on bench in a one-pass (1P) configuration using images of an E-letter projected on the retina of the model eye, obtained with a CCD camera placed at the retinal plane (Fig. 1, top rows), and double-pass (2P) configuration using images of a point-source projected on a diffuser acting as retina, captured with a CMOS camera optically conjugated with the retina (Fig. 1, bottom rows). Figure 1 illustrates the TF images obtained in the No IOL condition (A), the images obtained when projecting the light through the Isopure IOL with additional +0.2µm of spherical aberration (B), images through Isopure with no additional aberration (C), and the images through the Isopure IOL with additional -0.2 µm spherical aberration (D), showing qualitatively the depth-of-focus expansion in the Isopure IOL conditions.

Figure 2 A and B shows the TF optical quality measured on bench in all tested conditions with the 1P and the 2P metric, respectively. Both metrics reveal a clear expansion of the DOF in all conditions with the Isopure IOL, particularly on the AO and the negative SA conditions. The

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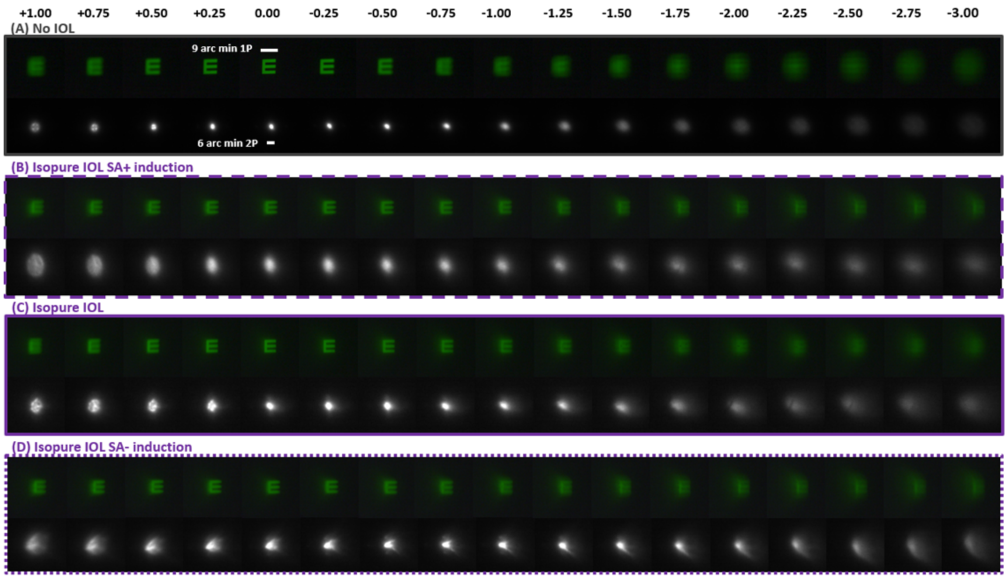

Fig. 1. Through-focus series, in a range of 4D in 0.25D steps; of single-pass images of an E-letter stimulus (top images) and double-pass images of a spot (bottom images) in an artificial eye, through (A) no-IOL condition; (B) Isopure IOL in a cuvette with positive spherical induction (+0.2 µm); (C) Isopure IOL in the cuvette and an aberration-free eye and (D) Isopure lens in combination with -0.2 µm spherical aberration induced on the DM.

IOL impose a slight degradation at far that is visible using both metrics and all conditions (0.08 on average for 1P and 0.06 on average for 2P, red bars in Fig. 2 C), and produce a benefit at intermediate/near (0.06 on average for 1P and 0.08 on average for 2P, green bars in Fig. 2 C). The benefit is lowest with induced positive SA.

3.2. Experimental through-focus visual quality (in subjects)

Figure 3 (A) shows the wave aberrations maps of all subjects participating in the under (natural aberrations, No IOL condition, top row) and the quality of the AO-correction (bottom row). The subjects have been ordered by increasing Root Mean Square (RMS) wavefront error (as shown in Fig. 3 (B). RMS ranged from 0.13 to 0.5 µm, and decreased below 0.1 µm in all cases (0.07 on average), for 4.5-mm pupils. Figure 3 (C) shows the amount of native spherical aberration in all subjects.

Figure 4 shows the TF VA in all subjects and conditions. With natural aberrations (Fig. 4 (A)) the presence of the Isopure IOL (purple lines) decreases the quality at far with respect to the no IOL (grey lines), although on average across subjects, the decrease is not statistically significant, and expands the DOF from 1.30 D (no IOL) to 1.53 D. With natural aberrations, the largest DOF expansion with the IOL occurred for subjects S6 and S7 (from 1.10 D to 1.65 D, and from 0.9 D to 1.65 D, respectively). AO-correction of aberrations (red lines) or leaving the natural aberrations uncorrected (purple line) did not change the average performance of the IOL, on average (Fig. 4 (B)). Individually (Fig. 4 (C)) AO-correction only improved peak performance over the natural conditions with the IOL in S8 (by 0.19 LogMAR), while in subjects S2, S4 and S7 performance with the IOL was actually better with the natural aberrations than with AO-correction (by -0.08, -0.04 and -0.11 LogMAR). Incidentally in S4 and S8 the presence of additional positive spherical aberration (SA+) reduces the expansion of DOF with the IOL, while in S2, S4, and S7, it is the presence of additional positive spherical aberration (SA+) expansion

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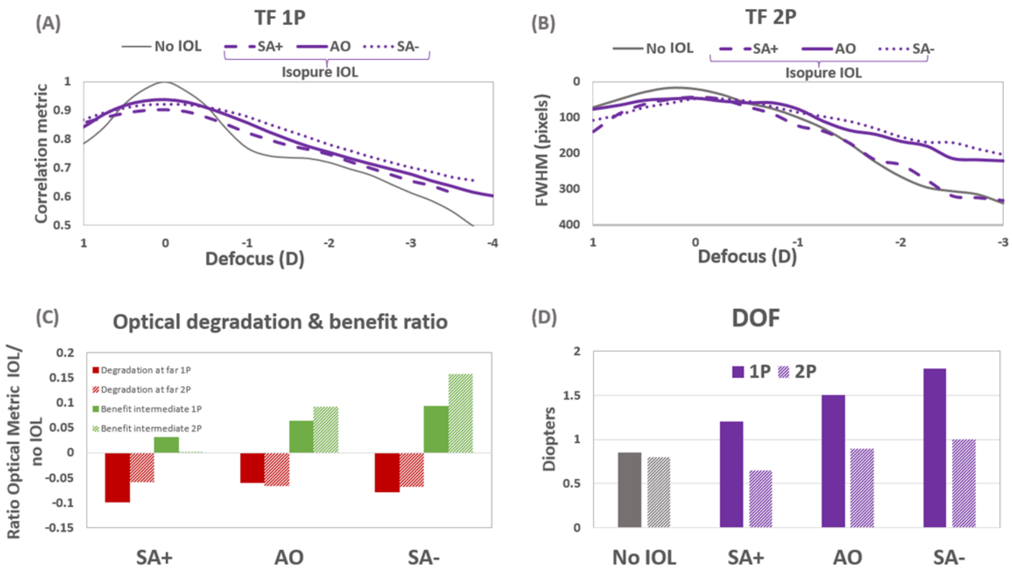

Fig. 2. Through focus optical quality for the 4 tested conditions (No IOL, Isopure IOL in cuvette with no additional aberration, AO; Isopure in cuvette with additional positive spherical aberration, SA+, and Isopure in cuvette with additional negative spherical aberration, SA-). (A) TF optical quality correlation metric (from one-pass E-letter stimulus, 1P); (B) TF FWHM (from double-pass images, 2P, 0.16 arcmin per pixel); (C) Optical quality ratio with IOL relative to the no IOL condition, at far (optical degradation) and at intermediate (optical benefit). (D) Optical depth of focus (DOF), estimated from the TF curves using 1P (solid bars) and 2P (shaded bars) metrics. Data are for 4.5 mm, monochromatic light (555 nm) and induced spherical aberration (positive or negative) was 0.2 µm.

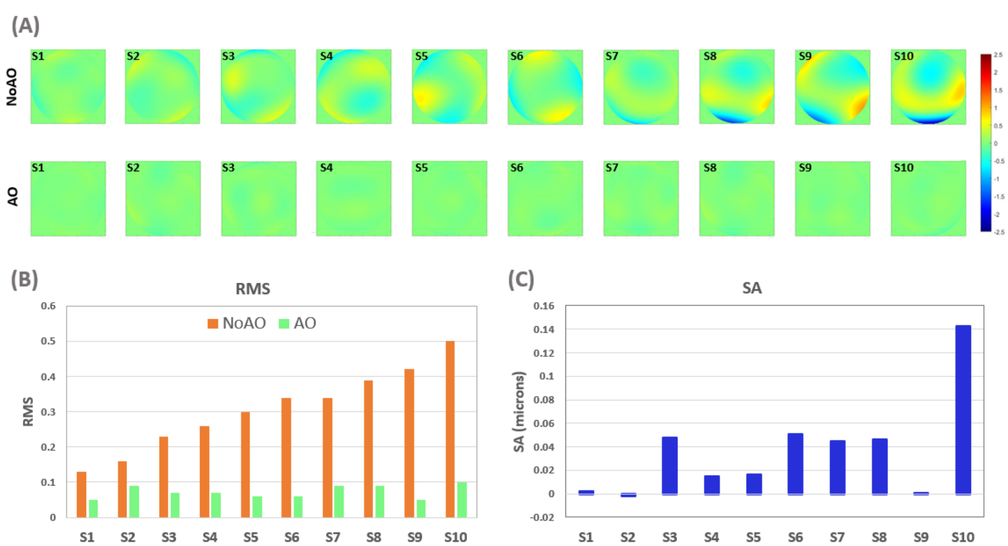

Fig. 3. (A) Wave aberration maps for Natural aberrations (top panels) and AO-corrected aberrations (bottom panels) for all 10 subjects (scale bar in microns) (B) Root Mean Square Wavefront error (RMS) with (AO) and without corrections (NoAO) of the natural aberrations of the eye. (C) Natural Spherical Aberration. Data are for 4.5-mm pupil diameter.

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of the presence of additional negative spherical aberration (SA-) which reduces the DOF with the IOL (Fig. 4(C), corresponding individual panels). However, in general the TF performance with the IOL appears to be primarily driven by the IOL design, and the role of the individual (and corrected/induced) aberrations was secondary. The intersubject variability of the TF curves (averaged across defocus positions) was not larger in the AO (-0.06 LogMAR) than in the NoAO conditions (-0.07 LogMAR).

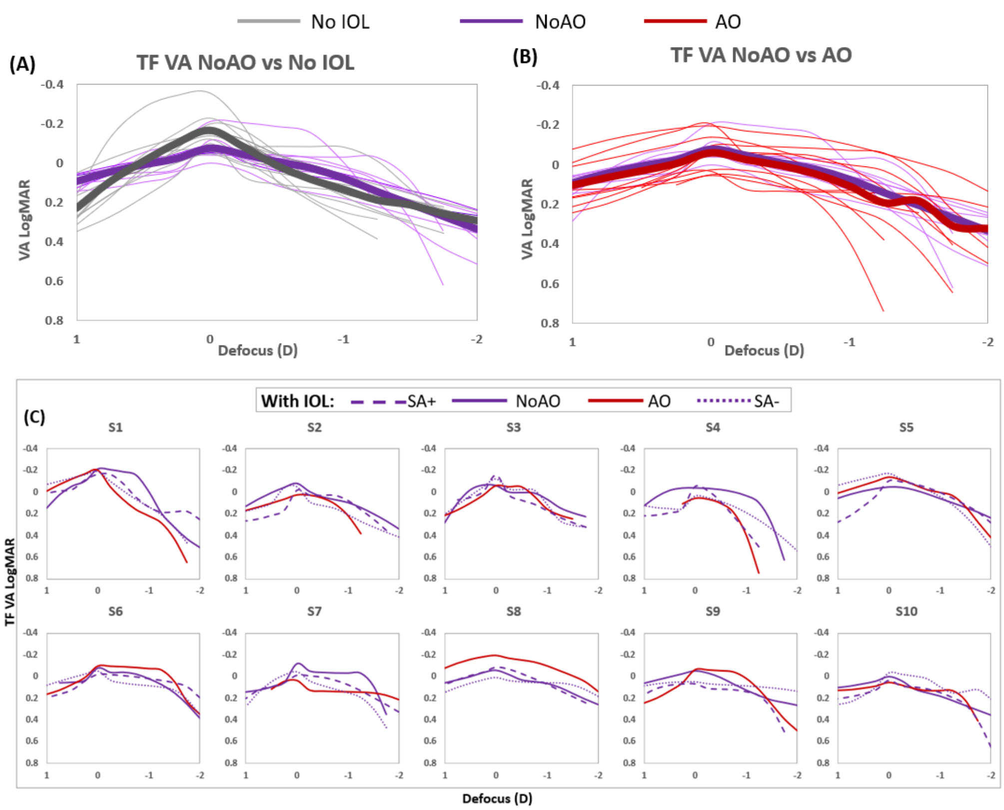

Fig. 4. Through Focus Visual Acuity, all eyes (A) All eyes with no IOL (grey lines), and with IOL (purple), under natural aberrations in all cases. (B) All eyes with IOLs, under natural aberrations (purple lines) and under AO-correction. In A and B thin lines represent individual subjects, and thick lines represent averages across subjects (C) All 10 eyes, in each panel, with IOLs, and 4 conditions: natural aberrations (purple solid line), corrected aberrations (red line), induced positive spherical aberration (SA+, dashed line), induced negative spherical aberration (SA-, dotted line).

Figure 5 (A) shows the DOF, on average across subjects, for all conditions. The presence of the Isopure IOL produced an increase in DOF by 0.20 D on average. On average, the expansion of DOF was largely independent on the presence or correction of high order aberrations, and induction of positive or negative spherical aberration (0.2 D with natural aberrations, 0.3 with AO, 0.25 with positive SA and 0.15 with negative SA), although some intersubject variability occurs. Visual Acuity at far (Fig. 5 (B)) was significantly better with no IOL, although it was on average above 0 (and in all subjects for the NoAO condition). Also, there was no statistically significant differences in the VA at far with the IOL across the different aberration conditions. Figure 5 (C) shows visual degradation at far and visual benefit at intermediate (1.25 D), in terms of LogMAR difference from the No IOL condition. Visual Degradation at far was lowest and visual benefit at intermediate was highest for the NoAO condition.

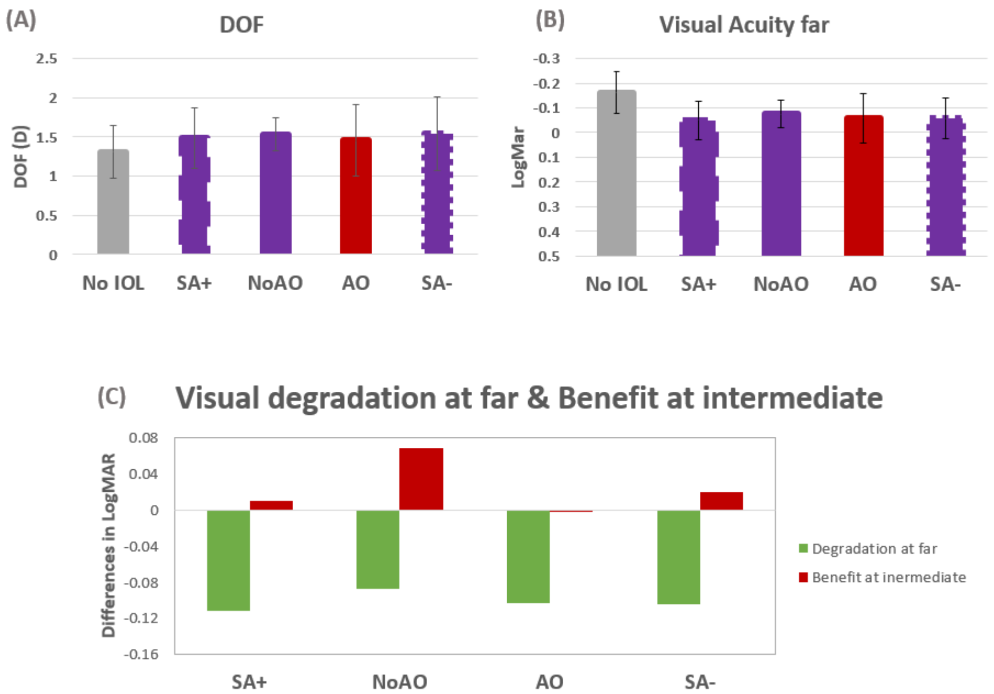

Fig. 5. (A) DOF estimated from the TF VA curves of Fig. 4, as the negative dioptric range above which LogMAR is better than 0.2. Results are average of the DOFs calculated across subjects for each condition (B) LogMAR VA at far, averaged across subjects for each condition (C) Visual degradation at far (green) and visual benefit at intermediate (1.25 D) as LogMAR differences with respect to the No IOL condition, averaged across subjects for each condition.

4. Discussion

In this study, we explored the effect of combining high order aberrations (natural, corrected or induced positive or negative spherical aberrations) on the optical and visual performance with a commercial Extended depth-of-focus (a.k.a premium monofocal IOL), the Isopure IOL (BVI-PhysIOL). Given that IOLs are designed for eyes with a generic cornea (of fixed geometry and aberrations) [27], understanding the performance stability to different amounts of natural aberrations in the eye is an interesting question. Visual simulators are an excellent tool to investigate visual performance with manipulated aberrations. Unlike computer eye models where, even if they customized to the subject's anatomy and 3-D biometry, can only predict retinal image quality, visual simulations allow direct measurement of visual performance under manipulated aberrations. Also, unlike measurements on pseudophakic subjects implanted with the IOL under investigation, visual simulators allow comparing different conditions in the eye of a subject. A standard clinical study would involve various groups of subjects classified, for example, by the magnitude of their corneal aberrations, although differences may be confounded by intersubject variability in the neural response, which is minimized by intra-subject testing of different aberration conditions, achieved with a DM in an AO visual simulator.

AO Visual Simulators have also been shown in the literature to replicate the design of different IOLs and predict pre-operatively the expected post-operative visual performance [4,5]. In previous studies, we have shown excellent correspondence between pre-operative measurements of TF visual performance through simulated IOLs mapped on a Spatial Light Modulator or SimVis) and post-operative data [4]. Also, we showed a good correspondence between TF visual performance through physical phase-plates [11] and physical IOLs immersed in a cuvette projected onto the eye and through an SLM or SimVis representing those IOLs. In recent work, we have proved the similarity between simulated IOLs and the projected IOLs of standard power (20-22 D) immersed in cuvette such that the optical base power of the lens is removed. One of these comparisons included the Isopure IOL which we further evaluate in the current work [12]. In this study, we opted by physically projecting the IOL-in a cuvette, and using the DM in an AO-visual simulator to correct the natural aberrations of the eye or to induce spherical aberration [28,29]. The test conditions (all including the Isopure IOL) were tested against the natural eye (i.e. with no IOL). This condition in phakic eyes with paralyzed accommodation mimicked a monofocal IOL, although some variability with respect to a true monofocal IOL might be expected associated to intersubject differences in the crystalline lens aberration Also, we adopted an absolute DOF metric for the through-focus VA curves (dioptric range above 0.2 logMAR VA) [25], and a standard relative DOF metric for the through-focus Visual Strehl on-bench [24], so only qualitative similarities in trends should be expected.

Consistent to its EDOF design, the Isopure IOL expanded depth of focus with respect to the no IOL condition, as shown both on-bench (Fig. 2) and in subjects (Figs. 4 and 5). Published studies of on bench performance of the Isopure IOL report 1 D DOF, and 50% DOF expansion compared to a monofocal IOL (the Micropure IOL, in that study). Those results are in agreement with our on-bench data: 1.50 D DOF for the correlation metric and 0.9 D DOF for the FWHM metric; and a 50% DOF increase with the correlation metric, which has been shown to best capture TF visual quality curves. These values are within the expected differences given the different experimental configurations (P-MTF measuring device by Lamda-X and ANSI-standard artificial eye in the prior report and IOL in cuvette, artificial eye and AO Visual simulator in our study). Also, differences are expected from the use of a different optical quality metric (MTF at 50 l/mm in the previous report) and the correlation metric/double pass image FWHM in our study. In subjects, we found an increase of DOF by 0.23 D (No IOL: 1.30 ± 0.33 D; NoAO + IOL: 1.53 ± 0.21), which compares with the 0.25 D increase reported by Bova et al in a study [15] on 84 subjects implanted binocularly with the Isopure IOL and a monofocal IOL (12 months post-op), from binocular photopic VA defocus curves, and the reported 1.5 D DOF. The similarity is remarkable, despite some differences between our study and that of Bova et al, including our younger cohort (mean age in their study was 71.33 ± 7.91 and 29.8 ± 3.4 years in our study), pupil diameter (natural pupil on their study and dilated), a comparison with an aspheric monofocal IOL (TECNIS PCB00 IOL (Johnson and Johnson Vision, AMO Groningen BV)), and their results after 12 months post-operative and binocular.

Our visual performance results also agree well with those in 18 pseudophakic subjects implanted with the Isopure IOL from a recent study by Stodulka et al [16]. The reported post-op VA in that study was -0.02 LogMAR binocular at far, and 0.14 LogMAR binocular at 1.25 D (80 cm), to be compared with our -0.07 ± 0.05 log MAR at far and 0.12 at 1.25 D (NoAO + IOL condition). The slightly better performance in our group may be associated to our use of monochromatic light (in a previous study we showed a comparable gain from using monochromatic instead of white light illumination for targets viewed monocularly than from binocular summation for targets viewed binocularly [4], or our younger group, compared to a post-cataract surgery population (69.4 ± 6.9 years in Stodulka et al). The slight decrease of performance at far (less or equal at 10% in optical performance for on bench measurements, Fig. 2, and less than 0.1 LogMAR on average, in VA in subjects (Fig. 5), is compensated by a gain at intermediate and near distances (Fig. 2 and 5, for on bench and subjects, respectively).

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The use of AO allowed us to test the impact of aberrations on the performance of the Isopure IOL. On bench data (on an artificial eye with no aberrations) showed a relatively minor impact of the induced aberrations over the lens design (Fig. 2). The IOL produced an expansion of DOF regardless the absence of aberrations or presence of positive or negative spherical aberration. Although this IOL design is not particularly driven by 4th order spherical aberration (the high order aspheric coefficients introduce also high order spherical term and a smooth alternation of far and intermediate zones across the pupil), some induction of negative spherical aberration is expected. While this potential interaction does not appear to be captured in the correlation metric (induction of positive spherical aberration, SA+, does not seem to counteract the negative spherical aberration of the lens and improve optical quality over the AO or the SA- condition), it may be behind the slightly narrower DOF with SA + captured by the FWHM metric.

The intersubject variability (in natural aberrations and neural response) appears to dissipate those trends, and on average, there is no difference in DOF, and at far or near performance in absence or presence of positive or negative SA. The tolerance of the Isopure IOL to high order aberrations and to spherical aberration expands previous findings in subjects that show that the performance of this lens is tolerant to the induction of astigmatism [30]. A previous study of various multifocal IOLs on bench [31] showed that the DOF increase with multifocal IOLs was attenuated when more than 0.75 D astigmatism remained uncorrected. However, given the different refractive design of the lens under study it is not likely that this result holds for this lens. Our subject data indicate a higher prevalence of the IOL design over the individual's aberrations on both visual acuity at far and DOF. Also, multiple studies have found a degradation of VA and an expansion of DOF when spherical aberration is induced [25,30]. However, an impact on DOF is expected when aberrations are corrected or induced on virgin eyes, they do not appear to occur in combination with the Isopure IOL. As found on bench, correcting or inducing aberrations have little impact on performance in combination with the IOL. On average, while there is a significant reduction in Visual Acuity at far in presence of the IOL with respect to the no-IOL condition, the differences in VA across different aberration conditions are not statistically significant, nor the effects on DOF. Individually, however, there were some subjects where performance was more influenced by induction of positive or negative spherical aberration or correction of high order aberrations. However, we did not find a straightforward relation of this effect with the natural amount of spherical aberration, or overall optical quality in these subjects.

The study further demonstrates the use of AO visual simulators to understand prospective performance with IOLs prior to intraocular lens implantation. While in this study the IOL was inserted in a cuvette and projected on the subject's eye, as it was designed to evaluate the impact of aberrations on the lens performance, and not the quality of the IOL simulation, the multi-channel nature of the system would have allowed simulating the IOL in, for example the SLM (as done in prior studies) while manipulating the aberrations of the eye with the DM. The results of our study indicate that the tested IOL is tolerant to the induction and correction of aberrations, suggesting that this IOL could be used in a large proportion of the population (from almost perfect eyes to relatively large amounts of spherical aberrations) without significant differences in performance. More studies with a larger sample size and including patients in the age range of the average cataract surgery patient should be conducted to clarify the findings of the study. The simulated spherical aberration induction is consistent with that found in post-myopic LASIK (positive SA) and post-hyperopic LASIK subjects (negative SA) [18,19], indicating that the evaluated IOL could also be suitable (provided that the IOL power is adequately selected) in post-LASIK subjects.

A potential limitation of the study is the fact that it was conducted in a relatively younger population than the intended target for this lens. Since crystalline accommodation was paralyzed pharmacologically and the pupil limited by a 4.5 mm artificial pupil, two major properties of aging (presbyopia and pupillary miosis were mimicked). An older population may have shown a decline in VA from neural aspects [32] as well as shifts in the crystalline lens spherical aberration towards more positive values [33]. Since all conditions were tested in the same subjects, the reported relative effects (i.e. monofocal No IOL vs EDOF IOL) should not be influenced by neural resolution. On the other hand, given the little impact of relatively large amounts of spherical aberration, it is unlikely that age-related changes or individual differences in spherical aberration play a significant role in the described effects. In fact, in this young population, it is likely that the spherical aberration of the crystalline lens of the eye does not differ much from that of aspheric monofocal IOLs, which attempt to mimic the spherical aberration of the young lens. Therefore, the no IOL could be in fact representative of a monofocal IOL condition. On the other hand, Villegas et al. showed that, in general, the spherical aberration of the crystalline lens (present in pre-op visual simulations but removed in cataract surgery) plays a minor role in the simulated performance with IOLs conducted pre-operatively [34]. In any case, the described AO visual simulator has the capacity to remove the spherical aberration (although not the scattering) of the natural crystalline lens using the DM, for simulations in cases where that may play a role (i.e. monofocal aspheric IOLs aiming at correcting the aberrations of the cornea). This is particularly the case in our configuration with the cuvette, which is outside the AO closed-loop channel, and therefore can be bypassed in the correction.

In the practical use of visual simulators on cataract patients, simulations will be generally performed in the presence of scattering. In a recent study [35] we demonstrated that patients even with significant amounts of cataract (assessed with a double-pass based clinical instrument) ranked perceived quality with different simulated presbyopic corrections similarly pre-operatively (through scattering) than post-operatively (through a transparent monofocal IOL). Given the temporal multiplexing nature of the SimVis simulator used in that study, the image is not unevenly obstructed by crystalline lens opacities. In conventional AO systems, which project a spatial representation of the IOL, certain pupil areas more transmissive than others, which may impose some limitations in eyes with cataract.

The measurements reported in this study were performed with monochromatic light (555 nm) instead polychromatic light. Previous subjective and objective measurements of the DOF in the phakic human eye performed in monochromatic light (three wavelengths) and in polychromatic light, did not show significant differences of DOF across wavelengths, and only a slight increase in DOF with white light [24]. A recent on bench study on 5 different IOLs shows DOF broadening in the polychromatic with respect to monochromatic light, in particularly with the Isopure IOL [36]. Given previous findings in phakic eyes that, in presence of aberrations, DOF is only minimally affected by pupil diameter, wavelength and spectral composition [24], and the tolerance of DOF with Isopure IOL to aberrations and pupil diameter, we do not anticipate chromatic aberration to play a large role, although this needs to be proved in measurements or simulations

Finally, the study did not consider the effect of potential adaptation to the natural high order aberrations of the eye [37]. Previous studies have shown that visual performance with natural high order aberrations (i.e. astigmatism or keratoconus) surpasses that of normal subjects through the same aberrations induced with AO [38–40] suggesting neural adaptation or perceptual learning to the long-term optical degradation. While potential differences in performance with the IOLs associated to natural or induced aberration (of the same amount) can only be tested in groups with naturally high positive or negative spherical aberration (i.e. the mentioned post-LASIK eyes) it is unlikely that our results are biased by this effect, as we did not find performance trends associated to the magnitude of the natural aberrations, and the measured effects appear dominated by the IOL design. The trend for larger benefit at near (and lower degradation at far) found for the Isopure IOL in combination with the natural aberrations of the eye, in comparison with other conditions, including fully corrected optics, could reflect some adaptation to the natural optics, or simply a result of the IOL design for eyes with normal amounts of aberrations. On the other hand, the fact that TF visual acuity curves in eyes with all aberrations corrected and through the

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same IOL show large differences in TF VA curves (even if the retinal image quality is identical in the entire dioptric range) suggest that neural factors are critical and further emphasize the importance of the visual simulation, beyond optical expectations.

5. Conclusion

AO simulators are a suitable tool to assess new IOL designs, EDOF IOLs, and predict the behavior in pseudophakic eyes before surgery.

Isopure EDOF IOL show a good balance between DOF (1.53 ± 0.21D) and visual acuity at far (-0.07 ± 0.05). All conditions tested with Isopure IOL (correcting ocular aberrations and inducing spherical aberration) show on average, higher values of DOF than the no IOL condition.

Isopure IOL presents a good balance between DOF and optical quality at different conditions tested, and in an experimental setting, it appears to be effective in a high range of subjects, including simulated post-LASIK subjects.

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Data availability. Data underlying the results presented in this paper are not publicly available at this time but may be obtained from the authors upon reasonable request.

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