LIGHT-ADJUSTABLE LENS: CUSTOMIZING CORRECTION FOR MULTIFOCALITY AND HIGHER-ORDER ABERRATIONS

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ABSTRACT

Purpose: To determine the feasibility of creating customized multifocal and aspheric patterns onto a light-adjustable lens (LAL) using a digital light delivery (DLD) system.

Methods: Silicone LALs were placed in a wet cell and irradiated in vitro using the DLD. Spatial intensity patterns were designed and generated to (1) create a multifocal optic with customized power and diameter and (2) simultaneously correct defocus and spherical aberration. In addition, the LALs were adjusted in vivo for defocus and spherical aberration using a rabbit model. Optical properties of the adjusted LALs were determined using a phase-shifting Fizeau Interferometer and a Shack-Hartmann wavefront sensor.

Results: In vitro creation of multifocal patterns demonstrated ability to reproducibly customize zone diameter and power. Both bull's-eye bifocal and annular patterns were successfully created on LAL. Central adds ranging from +2.0 to +3.5 D with zone diameters ranging from 1.5 to 2.5 mm were demonstrated with the bull's-eye pattern. Application of the annular pattern showed that an annular zone ranging from +2.25 to +2.8 D was written around either an unchanged or −2.5 D corrected LAL central 2-mm region. Spherical aberration was reduced simultaneously with correction of hyperopia and myopia, both in vitro and in vivo. Additionally, these customized spatial intensity profiles can be written onto an LAL that is first adjusted to emmetropia. The ability to readjust the LAL is demonstrated.

Conclusions: Customized multifocal optics were created in vitro on the LAL. Spherical aberration was reduced simultaneously with correction of defocus both in vitro and in vivo. Potential correction for higher-order aberrations was also demonstrated.

INTRODUCTION

The current generation of intraocular lens (IOL) technology, including multifocal, accommodative, and aspheric IOLs, demands greater refractive precision to provide maximal visual function. Despite advances in biometry, small-incision surgery, and astigmatic keratotomy, many patients require spectacles postoperatively to achieve emmetropia.[1-5] Patients are increasingly opting for keratorefractive procedures after implantation of these new-technology IOLs to achieve spectacle independence. This entails a second surgical procedure, often performed by another surgeon because most cataract surgeons do not perform refractive procedures such as LASIK. Furthermore, dry eye, a common complication of these corneal refractive procedures, can be more pronounced in this older cataract patient population. A potential alternative to wearing spectacles or secondary surgical refractive procedures after implantation of a multifocal or accommodative IOL is the use of a light-adjustable lens (LAL).[6-8]

The LAL contains photosensitive silicone molecules that enable precise and noninvasive postoperative adjustment of refractive power using ultraviolet light. The LAL formulation consists of four basic components: silicone matrix polymer, photoreactive macromer, photoinitiator, and UV absorber. The LAL material design has been described previously[6,7] and is based upon the principles of photochemistry and diffusion whereby photoreactive macromers dispersed within the cross-linked silicone lens matrix are photopolymerized upon exposure to UV light (365 nm) of a select spatial intensity profile. Upon irradiation, the photoinitiator initiates polymerization of the macromer photoreactive groups to form an interpenetrating polymer within the lens matrix.[9] Diffusion of the remaining unirradiated macromer into the irradiated areas induces a change in shape or refractive index, or both, to produce a predictable power change.

Silicone was selected as the lens matrix because of its optical clarity, ability to be folded through a small incision during insertion, high diffusibility (ie, a low glass transition temperature), and history of safe use in IOLs. In addition to the UV-absorbing properties of the LAL, the posterior surface of each lens is molded with a 50-µm-thick higher-UV-absorbing layer to impart the pseudophakic patient with additional UV protection for the retina during the irradiation treatment procedure.[10]

By controlling the irradiation dosage (ie, beam intensity and duration), spatial intensity profile, and target area, physical changes in the radius of curvature of the lens surface are achieved, thus modifying the refractive power of an implanted LAL to add or subtract spherical power, eliminate astigmatic error, or correct higher-order aberrations. Once the appropriate power adjustment is achieved, the entire lens is irradiated in a second irradiation procedure, referred to as "lock-in." By irradiating the entire lens, any remaining unreacted macromer is polymerized and macromer diffusion is prevented; thus, no change in lens power results.

Clinically, changes in LAL power are accomplished using a digital light delivery (DLD) system engineered by Carl Zeiss-Meditec (Jena, Germany). The DLD (Figure 1) consists of a UV light source, projection optics, and control interface built around a standard

slit lamp. The light source employed is a mercury (Hg) arc lamp delivered to the projection optics through a liquid-filled light guide. The light source includes a narrow bandpass interference filter producing a narrow-wavelength beam with a center wavelength of 365 nm. The DLD contains a digital mirror device, which is a pixelated, micromechanical spatial light modulator formed monolithically on a silicon substrate. The advantage of the digital mirror device is the ability to easily define a specific high-resolution spatial intensity profile, program this into the digital mirror device, and then irradiate the LAL.

FIGURE 1
Digital light delivery device (Carl Zeiss-Meditec).

The DLD is designed for controlled alignment of the adjustment and photolocking beam with the LAL. The DLD projects an alignment reticle image to the surgeon's eye through a common optical path shared with the UV light projection optics. The patient participates in alignment by attending a fixation target, parcentral to the delivery beam.

Multifocal, accommodative, or aspheric IOLs can incorporate the light-adjustable material to impart the ability for postoperative refractive optimization. Alternatively, the multifocal or aspheric optic could be "written" on the LAL in situ using the DLD. Specifically, a monofocal LAL could be implanted and postoperatively corrected for emmetropia. A customized multifocal pattern can be added onto the LAL with a second adjustment. Similarly, an aspheric correction could be written on an LAL that is first adjusted to emmetropia. The LAL could allow for the customization of the size and location of the added pattern(s) to the patient's specific visual axis and pupil dilation response, thus mitigating untoward effects of decentration well described in the wavefront of these IOLs.[11,12]

To test whether a customized optic could be written onto a monofocal LAL, preliminary feasibility studies using the DLD and the silicone LAL were performed.

METHODS

IN VITRO IRRADIATION AND OPTICAL CHARACTERIZATION

The experimental apparatus depicted in Figure 2 was constructed to develop the irradiation conditions for the LAL in vitro. There are two main components in this optical instrument: (1) the illumination and projection system, composed of a mercury (Hg) arc lamp filtered to 365 nm and a digital mirror device, and (2) an optical analysis system, previously described,[7] utilizing a phase-shifting Fizeau Interferometer (Wyko Model 400) operating in double-pass configuration fitted with a 4-inch transmission sphere.

Knowledge of the spatial intensity profile applied to the LAL coupled with the analysis of the altered wavefront allows guidance in the modification of the pattern to produce the desired changes. Typical average intensity at the LAL and irradiation times for adjustment is 12 mW/cm^2 and 40 to 120 seconds, respectively. A minimum of eight LALs were irradiated for each dose (spatial intensity profile, intensity, and time) to establish reproducibility in power change and optical quality.

IN VIVO IRRADIATION USING A RABBIT MODEL

The rabbit study was conducted at the University of Utah. Eight New Zealand white rabbits weighing between 2.4 and 3.2 kg were acquired and treated in accordance with guidelines set forth by the Association for Research in Vision and Ophthalmology and the Animal Welfare Act regulations.
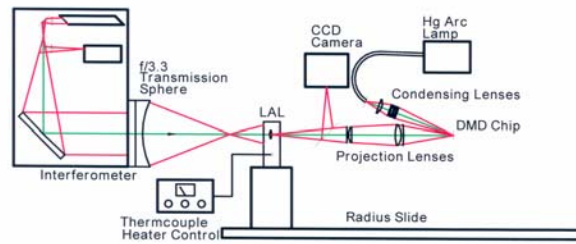
FIGURE 2

Schematic diagram of the interferometer/irradiation system. Reprinted from Schwartz DM, et al.[7]

Following induction of general anesthesia, the lens was removed by phacoemulsification. A viscoelastic was used to inflate the capsular bag, and the folded LALs were inserted into the capsular bag. Combination antibiotic- corticosteroid ointment (neomycin and polymyxin B sulfates, and dexamethasone) was applied to the eyes following surgery.

At 1 day postimplantation, the rabbits were anesthetized and placed into a custom-built Plexiglas box attached to a standard camera tripod to allow for accurate alignment of the irradiation treatment beam with the implanted LAL. Prior to irradiation, a custom-designed contact lens (Ocular Instruments, Bellevue, Washington) was coupled to the rabbit's eye using a 1.5 wt% methylcellulose solution to maintain an optically smooth surface for irradiation. The implanted LALs were then irradiated using the DLD with appropriate spatial intensity profiles and doses.

RESULTS

MULTIFOCAL LAL

Multifocal Bull's-eye Design

After first bringing the LAL patient to emmetropia with an initial adjustment using the DLD, the ophthalmologist can impart multifocality to the LAL by treating the LAL with a second adjustment. This treatment scheme is illustrated in the series of interferograms in Figure 3 depicting the addition of a "bull's-eye" type bifocal lens design after an initial adjustment to emmetropia. Figure 3 (left) displays the interference pattern of the unirradiated monofocal LAL at its preirradiation best focus position along the optical axis of the interferometer. Assuming the patient was 2.0 diopters (D) myopic, the implanted LAL was given a −2.0 D correction to achieve emmetropia. Figure 3 (center) shows the interference pattern of the LAL at the original preirradiation best focus position 24 hours after irradiation treatment corresponding to an induced spherical correction of −2.0 D.

Figure 3 (right) demonstrates a 2-mm central zone of +2.0 D add as a result of the second adjustment. This experiment demonstrates the ability to readjust the LAL after the initial adjustment to emmetropia with a second adjustment for a multifocal add prior to the lock-in treatment.
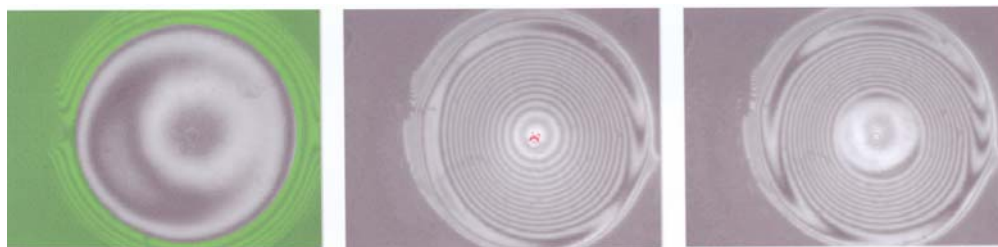

FIGURE 3

Interferograms of in vitro created bull's-eye design on light-adjustable lens (LAL). Interference fringes for (left) nonirradiated LAL at the preirradiation best focus position; (center) the LAL shown at left, after adjustment and removal of −2.0 D of power from the LAL, as indicated by the defocus fringes; and (right) the LAL shown at center, after the addition of +2.0 D in the central 2 mm of the lens. All of these interferograms were recorded at the same position along the optical axis of the interferometer for direct comparison.

To illustrate the potential for creating a customized bull's-eye type bifocal on the LAL, lenses were irradiated with varying-diameter beam sizes and durations. Table 1 summarizes the dioptric range and zone size developed for the bull's-eye design. Listed

in each cell of this nomogram matrix is the average dioptric power change and the first standard deviation in parenthesis for a given zone diameter.

TABLE 1. IN VITRO BULL'S-EYE BIFOCAL LIGHT-ADUSTABLE LENS NOMOGRAM MATRIX*

ZONE SIZE (MM)	POWER CHANGE AT SPECTACLE PLANE			
	2.00 D	**2.50 D**	**2.75 D**	**3.00 D**
1.50	NA	NA	+2.79 D (0.18 D)	+3.11 D (0.12 D)
1.75	+2.18 D (0.14 D)	+2.42 D (0.16 D)	+2.85 D (0.10 D)	+2.98 D (0.13 D)
2.00	NA	+2.36 D (0.08 D)	+2.74 D (0.15 D)	+3.20 D (0.18 D)
2.50	+1.98 D (0.06 D)	+2.52 D (0.09 D)	+2.68 D (0.05 D)	+3.08 D (0.07 D)

NA = Not available.
*Each cell represents average and standard deviation (in parenthesis) of power change of eight light-adjustable lenses irradiated at a specified zone diameter.

Representative LALs with central add of different powers and affected zone diameters as a result of multifocal adjustment are presented in Figure 4. The postirradiation fringes of an LAL at its preirradiation best focus position is displayed (Figure 4, top left).
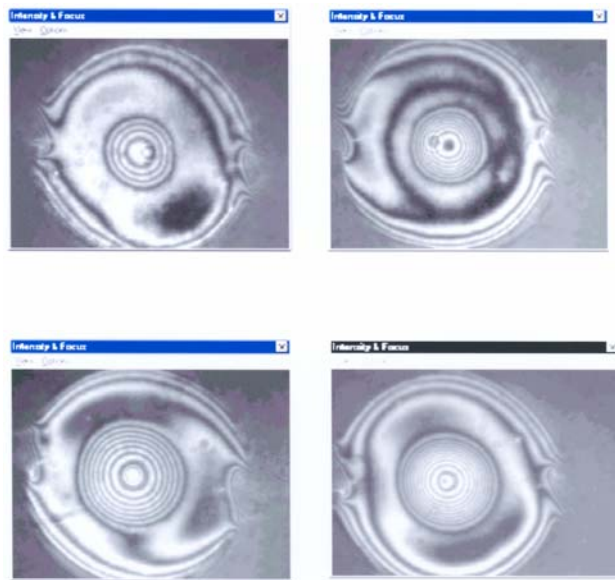

FIGURE 4

Interferograms of in vitro created bull's-eye design of different power adds and specified affected specified diameters on light adjustable lens (LAL). Interference fringes for (top left) an LAL after the addition of + 2.1 D of power over an affected zone of 1.8 mm; (top right) an LAL after the addition of + 3.5 D of power over an affected zone of 2.0 mm; and (bottom, left and right) LALs with addition of +2.1 D and +3.2 D, respectively, both with an affected central zone of 2.5 mm.

Inspection of this image shows the appearance of approximately four fringes (in double pass) of optical path difference in the central 1.8-mm region of the LAL. The measured power change in this region corresponds to approximately +2.1 D referenced to the spectacle plane. Further analysis of this fringe pattern shows that the region outside this add power zone is unaffected with no power change. Figure 4 (top right) shows an add zone diameter of 2.0 mm with +3.5 D of power. Figure 4 (bottom left) shows an add power of +2.0 D over a central 2.5-mm region, and Figure 4 (bottom right) shows an add power of +3.2 D over a 2.5-mm region.

The results demonstrate that the bull's-eye bifocal LAL can be created with precise control of the refractive power added as well as the size of the imprinted zone.

Multifocal Annular Ring Design

The annular ring design is similar to the bull's-eye configuration LAL in that the size and refractive power added by the annular ring may be customized for each patient, but also has the advantage of removing the potential problem of unintended myopia as observed with patient pupil constriction under bright light conditions (eg, driving west at sunset).

Figure 5 (top left) shows the fringe pattern of the LAL nulled over a 4-mm aperture prior to irradiation. This LAL was irradiated with the appropriate annular profile producing the resultant fringe pattern at the preirradiation best focus position (Figure 5, top right). Inspection of these fringes indicates that the central region (~1.9-mm diameter) of the LAL has been unaffected, as noted by the absence of any change in the optical path difference in this region. However, the region directly around this central region shows the buildup of several closely spaced fringes in a 0.5-mm-wide annular ring pattern. Translating the LAL along the axis of the interferometer toward the point source produced by the transmission sphere until the power in the fringes of the annular ring has been nulled allows determination of the resultant power change (Figure 5, bottom left). Using this method in conjunction with the Crystal Wave IOL test bench (Wavefront Sciences, Albuquerque, New Mexico) indicates that ~+3.3 D has been added to the LAL base power in this annular ring region. This corresponds to approximately +2.3 D at the spectacle plane. Figure 5 (bottom right) shows the same LAL at the same preirradiation position as Figures 5 (top left) and 5 (top right) with tilt added across the fringe pattern. Inspection of the linearity of the fringes between the central region and the region outside the annular zone again shows the similarity in power between these two distance zones.
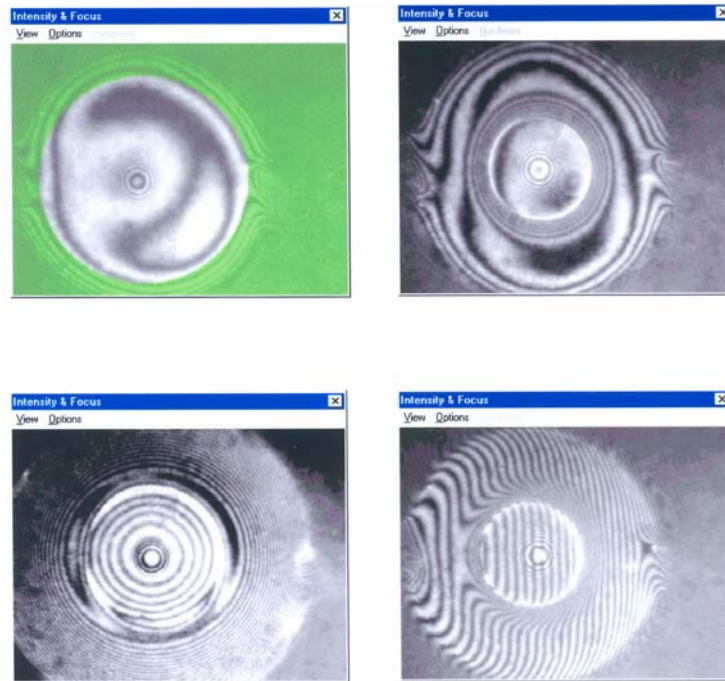

FIGURE 5

Interferograms of in vitro created annulus add on light-adjustable lens (LAL). Interference fringes for (top left) the LAL at the preirradiation best focus position along the axis of the interferometer (4-mm aperture); (top right) postirradiation interference fringes of the LAL at the preirradiation best focus position; (bottom left) postirradiation interference fringes of the LAL translated along the optical axis of the interferometer until the power in the annular region has been nulled; and (bottom right) postirradiation interference pattern at the preirradiation best focus position. Tilt has been added across the wavefront to help visualize the different zones of power.

The irradiation duration was changed to produce an annulus add zone of approximately +2.8 D at the spectacle plane with a width of 0.6 mm. The interferograms of the LAL representing this feature are displayed in Figure 6. The central 1.8-mm region has undergone no power change.

Another demonstration of the in situ created annular design is shown in Figure 7. The LAL was irradiated with a spatial intensity profile to produce a negative adjustment in the central 2-mm zone of the lens with a positive add zone in the adjacent 1-mm annulus and no power change in the region immediately outside this annular zone. The resulting power change in the central 2-mm region corresponds to −2.5 D, and the power change in the 0.5-mm-wide annulus is measured as + 2.8 D, both at the spectacle plane. As evidenced by the interference fringes, the power in the region outside the annulus has not been altered. The clinical utility of this particular irradiation scheme could be beneficial for a patient who does not dilate beyond 3.0 to 3.2 mm even under low lighting conditions and who requires a postimplantation LAL negative power adjustment to achieve emmetropia.
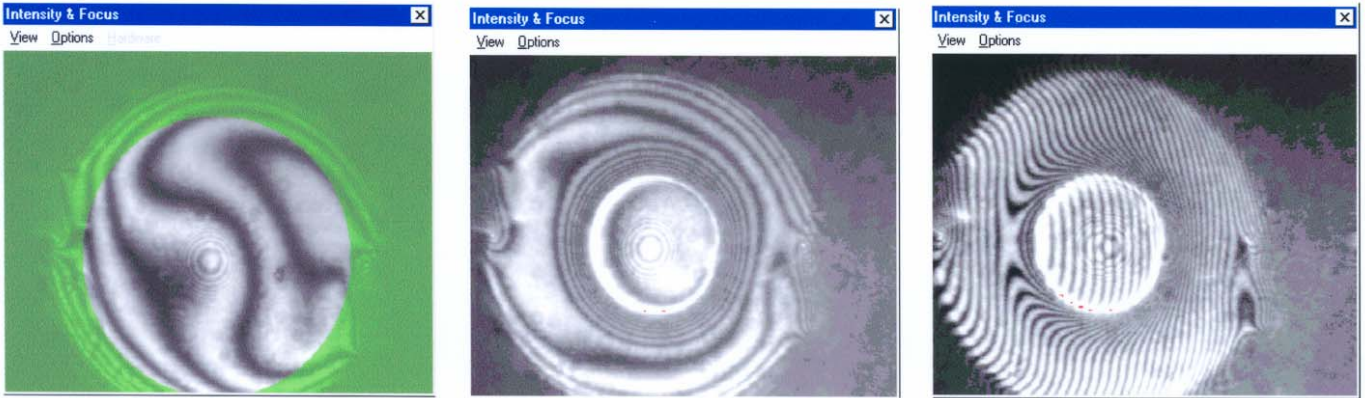
FIGURE 6

Interferograms of in vitro created positive annulus add on light-adjustable lens (LAL). Interference fringes for (left) the LAL at the preirradiation best focus position along the axis of the interferometer (4-mm aperture); (center) postirradiation interference fringes of the LAL at the preirradiation best focus position; and (right) postirradiation interference pattern at the preirradiation best focus position. Tilt has been added across the wavefront to help visualize the different zones of power.

FIGURE 7

Interferograms of in vitro created annulus add with central myopic correction on (negative center and positive annulus combination) light-adjustable lens (LAL). Left, Interference fringes for the LAL at the preirradiation best focus position along the axis of the interferometer (4-mm aperture). Center, Postirradiation interference fringes of the LAL at the preirradiation best focus position. Right, Postirradiation interference pattern at the preirradiation best focus position. Tilt has been added across the wavefront to help visualize the different zones of power.
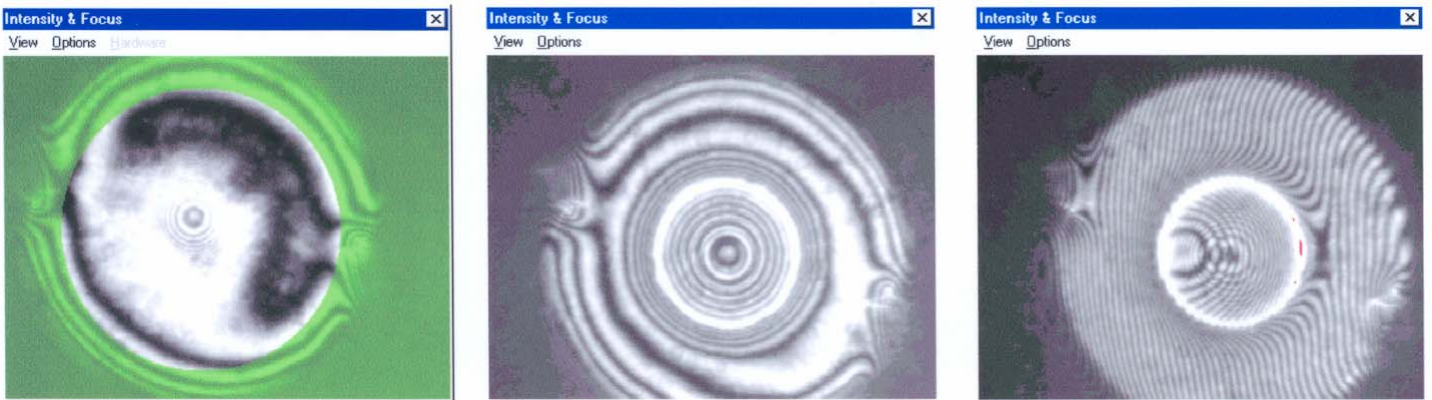
ASPHERIC LAL

Creating Aspheric Optic In Vitro

Table 2 shows the results for a set of 32 LALs irradiated with the same hyperopic treatment conditions (spatial intensity profile, intensity, and duration). The spatial irradiance profile used for these hyperopic adjustments is displayed in Figure 8. Inspection of this profile indicates some of the representative profile design parameters to produce an increase in lens power (intensity peaked in the middle) with a simultaneous creation of an aspheric optic (optimized "wings" at the edges of the profile). The results in Table 2 demonstrate reproducible spherical power changes with a reduction in the inherent spherical aberration from 0.34 D to 0.01 D.

TABLE 2. POWER CHANGE AND SPHERICAL ABERRATION DATA OF 32 LIGHT-ADJUSTABLE LENSES AS A RESULT OF SIMULTANEOUS CORRECTION OF BOTH HYPEROPIA AND SPHERICAL ABERRATION*

POWER CHANGE POSTIRRADIATION	AVERAGE SPHERICAL ABERRATION PREIRRADIATION (4-MM APERTURE)	AVERAGE SPHERICAL ABERRATION POSTIRRADIATION (4- MM APERTURE)
+1.45 ± 0.07 D	0.34 ± 0.03 D	0.01 ± 0.11 D

*The starting power of the lenses preirradiation was nominally +20.0 D.
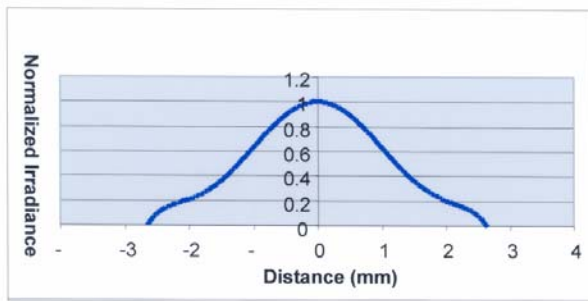

FIGURE 8

Hyperopic/aspheric adjustment spatial intensity profile. Left, Cross-sectional plot of the spatial irradiance profile used for hyperopic adjustments. Right, Grey-scale bitmap image programmed into the digital mirror device.

Table 3 displays the results for a set of 72 LALs adjusted for a −1.25 D myopic treatment. Inspection of the preirradiation and postirradiation spherical aberration values indicates that the treatment procedure removed approximately half of the spherical aberration initially present in the lenses.

TABLE 3. POWER CHANGE AND SPHERICAL ABERRATION DATA OF 72 LIGHT-ADJUSTABLE LENSES AS A RESULT OF SIMULTANEOUS CORRECTION OF BOTH MYOPIA AND SPHERICAL ABERRATION*

POWER CHANGE POSTRRADIATION	AVERAGE SPHERICAL ABERRATION PREIRRADIATION (4-MM APERTURE)	AVERAGE SPHERICAL ABERRATION POSTIRRADIATION (4-MM APERTURE)
−1.29 ± 0.16 D	0.38 ± 0.03 D	0.18 ± 0.09 D

*The starting power of the lenses preirradiation was nominally +20.0 D.

Creating Aspheric Optic In Vivo

Eight New Zealand white rabbits were implanted with +20.0 D LALs using standard surgical techniques as described in the "Methods" section. Six of the eight eyes were targeted for both myopic and spherical aberration corrections, and the remaining two were targeted for dual hyperopic and spherical aberration correction. The LALs were irradiated at 1 day postimplantation and then explanted at 1 day postadjustment. The LALs were analyzed interferometrically for any residual spherical aberration. Tables 4 and 5 summarize the results of the six negatively and two positively adjusted lenses, respectively.

The results in Table 4 indicate that the amount of spherical aberration present in the lenses was reduced by about one half while at the same time achieving adjustment of the lens base power. Table 5 indicates that in vivo positive adjustments produced lenses with negative spherical aberration, which can potentially act to null the inherent spherical aberration of the average cornea.

TABLE 4. SPHERICAL ABERRATION DATA OF SIX EXPLANTED LIGHT-ADJUSTABLE LENSES THAT WERE ADJUSTED SIMULTANEOUSLY FOR BOTH MYOPIA AND SPHERICAL ABERRATION CORRECTION IN RABBITS*

LENS NO.	RESIDUAL SPHERICAL ABERRATION (4-MM APERTURE)
1	+0.24 D
2	+0.19 D
3	+0.28 D
4	+0.17 D
5	−0.01 D
6	+0.07 D
Average	$+0.16 \pm 0.11$ D

*The starting spherical aberration is around +0.35 D.

TABLE 5. SPHERICAL ABERRATION DATA OF TWO EXPLANTED LIGHT-ADJUSTABLE LENSES THAT WERE ADJUSTED SIMULTANEOUSLY FOR BOTH HYPEROPIA AND SPHERICAL ABERRATION CORRECTION IN RABBITS*

LENS NO.	RESIDUAL SPHERICAL ABERRATION (4-MM APERTURE)
1	−0.18 D
2	−0.19 D

*The starting spherical aberration is around +0.35 D.

CORRECTION OF ADDITIONAL HIGHER-ORDER ABERRATIONS

To assess the ability of the LAL to correct additional higher-order aberrations in vivo, the Zernike aberration known as tetrafoil and described by the equation

$$S_4^4 = \left(4\rho^2 - 3\right)\rho^2 \cos 2\theta$$

was programmed into the digital mirror device and used to irradiate one of the implanted LALs . Figure 9 shows the grey-scale representation of the tetrafoil Zernike term that was applied to the LAL.
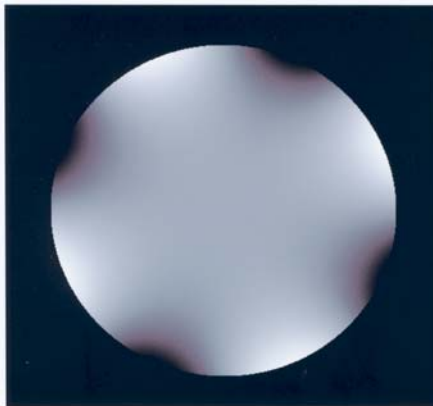

FIGURE 9

Tetrafoil grey-scale spatial intensity profile as programmed into the digital mirror device.

Figure 10 (left) depicts the raw interference fringes of the explanted LAL after irradiation with the tetrafoil spatial intensity profile. This figure demonstrates that the projected spatial intensity profile was reproduced on the wavefront of the LAL. As a further

illustration, the 3-D wavefront calculated from the interference fringes shown in Figure 10 (left) is displayed in Figure 10 (right), confirming the reproduction of the fourfold symmetry of the wavefront.
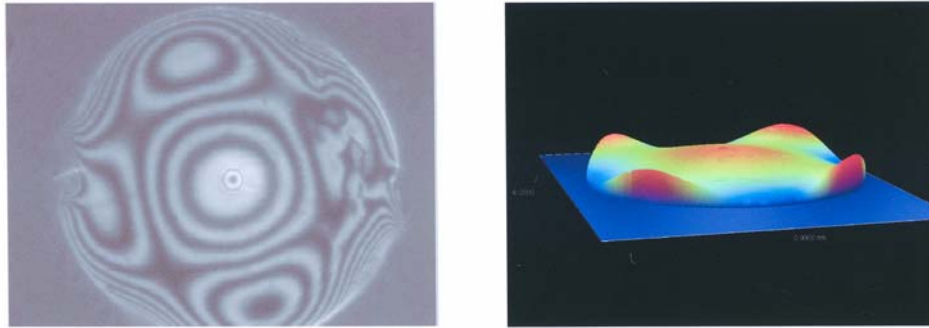

FIGURE 10

Explanted tetrafoil light-adjustable lens (LAL) from rabbit eye. Left, Raw interference fringes of the explanted LAL postirradiation with the tetrafoil spatial intensity profile. Right, 3-D wavefront rendering of the interference fringes shown at left.

DISCUSSION

We demonstrate feasibility of creating customized multifocal optics, aspheric optics, and correction for additional higher-order aberrations with the LAL using the DLD. Laboratory results confirm the ability to customize a multifocal pattern onto a monofocal LAL optic. Reduction of spherical aberration and the creation of a tetrafoil optic on the implanted LAL were demonstrated in an animal model.

Although recently commercialized IOLs are directed toward correction of presbyopia and enhancing visual function (contrast sensitivity), the inability to predictably achieve emmetropia following IOL implantation is potentially hindering the clinical adoption of this advanced IOL technology. Most podium presentations of presbyopic IOLs are accompanied by the importance of educating patients on the potential need for postoperative keratorefractive surgery to correct residual refractive error. Despite advances in biometry, IOL calculations, and small-incision cataract surgery, reliable prediction of postoperative refractive outcome remains difficult to achieve.

A recent study by Lawless (Implantation of AcrySof ReSTOR IOL: The Australian Experience, presented at AAO Annual Meeting, Chicago, 2005) illustrates how frequently optimized uncorrected vision is unachievable with multifocal IOLs despite careful preoperative biometry and patient selection. In a study of 84 patients implanted with Alcon's Restor diffractive IOL, only 30% possessed an uncorrected visual acuity (UCVA) of 20/20 at 3 months. However, 85% of these patients had achieved 20/20 best-corrected visual acuity (BCVA). A similar gap between UCVA and BCVA was shown with the Array multifocal IOL by Steinert and coworkers.[13] A customized multifocal LAL optic created in situ following an initial emmetropic adjustment can potentially enable patients to derive maximal benefit from IOL multifocality.

Optimization of visual function after implantation of a multifocal IOL is dependent on controlling several variables: astigmatism,[14] pupil size, and decentration.[15] The capability for in situ creation of a customized multifocal LAL centered on the visual axis may permit the surgeon to control these variables. Although we do not address correction of astigmatism in this report, we have previously performed astigmatic adjustments on the LAL in vitro[7] and in vivo (unpublished results). Furthermore, we are currently working on irradiation schemes to produce a three-zone adjustment that would allow simultaneous adjustments over multiple annuli, enabling treatment of both residual refractive error and multifocality in one irradiation.

An additional potential benefit of LAL technology demonstrated herein is the in situ creation of an aspheric optic centered on the visual axis. Although an IOL such as the Tecnis Z9000 has a modified prolate anterior surface to increase visual function by enhancing contrast sensitivity, the optical advantage is dramatically reduced with decentration as little as 0.4 mm.[12] Furthermore, the negative spherical aberration of the Tecnis IOL is derived from the mean positive corneal spherical aberration, as noted in a study of 71 patients.[16] As an alternative to taking an average spherical aberration as the basis of a "one size fits all" aspheric IOL, wavefront analysis and the DLD could be used to measure and correct a patient's specific spherical aberration, thereby establishing a customized method for spherical aberration correction.

In addition to correcting spherical aberration, the ability to create a tetrafoil optic in vivo suggests that higher-order aberrations could be corrected using LAL technology. Clinically, a wavefront measurement of the eye's aberrations could be made following refractive stabilization of the implanted LAL. The phase conjugate to these aberrations can be programmed into the digital mirror device to generate the appropriate spatial intensity profile and projected onto the LAL to correct the specific aberration.

In summary, we extend our previous observations on the capabilities of the DLD and demonstrate the ability to customize multifocal and aspheric corrections on the LAL. Although these early data are encouraging, extension into the clinical setting will likely require significant modification and optimization of the spatial intensity patterns, similar to what has been achieved for correction of defocus and astigmatism in our LAL clinical trials.

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PEER DISCUSSION

DR MARGUERITE MCDONALD. It does seem as if light adjustable IOLs (LALs) are a potential solution to virtually all of the problems posed by multifocal IOLs. These problems include the necessity for the predictable achievement of emmetropia; the need for perfect IOL centration; dealing with pre-existing astigmatism; variablility in patient pupil size; and patient tolerance of multifocality (with glare and loss of contrast).

These are well-designed studies, and the methods described are appropriate for the authors' *in vitro* and *in vivo* experiments. The results of both sets of studies are impressive, but more precise descriptions of some of the starting values are needed.

For instance, Table 2, which refers to the *in vitro* irradiation of 32 LALs for hyperopia and spherical aberration, has a legend which states: "The starting power of the lenses pre-irradiation was nominally +20.0 D." Another example of this lack of appropriate descriptors can be found in the figure legend for Table 3, which deals with the in vitro irradiation of 72 LALs for myopia and spherical aberration: "The starting power of the lenses pre-irradiation was nominally +20.0 D." The same sort of verbiage can be found in the figure legend for Table 4, which presents the spherical aberration data of six explanted LALs which were adjusted simultaneously for both myopia and spherical aberration correction in rabbits: "The starting spherical aberration is around +0.35 D." And the same lack of definition can be found in the legend for Table 5, which describes the spherical aberration data of two explanted LALs which were adjusted simultaneously for both hyperopia and spherical aberration correction in rabbits: "The starting spherical aberration is around +0.35 D."

The conclusions are clearly, concisely, and accurately stated, though it would have been preferable if some potential clinical problems had been addressed in the discussion. For instance, currently the patients must fixate on a target for 40 to 120 seconds for irradiation; isn't a tracker needed for submicron accuracy? And the details of the retinal toxicity experiments, while not the major focus of this paper, should have been briefly summarized in the introduction or the discussion, as readers would like to know how the 50 micron posterior lens coating was arrived at initially and then tested.

In summary, this is highly original work that has the potential to change the way we practice medicine in a significant way.

DR RONALD KLEIN: Were there any "before and after" quality of life measures that you included in your experiments?

DR RAYMOND APPLEGATE: I wonder about the repeatability. If you made 30 lenses in a row what kind of error bars would you have?

DR CHRISTIAN A. SANDSTEDT: With regards to Dr. Klein's question, the results presented in this paper are in-vitro and rabbit studies. A couple of different metrics that we use in the laboratory to assess the optical quality of the lenses (which will of course impact "quality of life") are measurements of the type and magnitude of the optical aberrations we have in the lenses post adjustment as well as the lens's optical resolving and contrast properties. To measure the optical aberrations we employ wavefront-sensing techniques such as interferometry and Shack-Hartmann style lenslet arrays. To measure the resolving ability and contrast of our lenses we image collimated bar targets (e.g. 1951 USAF Bar target) as well as measurement of the modulation transfer function (MTF). These measurements indicate that from an optical standpoint the LAL compares quite favorably to commercially available intraocular lenses

In response to Dr. Applegate's question, we do observe some deviation from the molded to our intended power. For a molded set of thirty, +20 diopters lenses we typically see a first standard deviation of ± 0.1 D. We have previously published in-vitro nomogram results showing that for a given power change, we observe a first standard deviation of ≤ 0.12 D from the mean (Schwartz D., et. al. Light-Adjustable Lens: Development of In-Vitro Nomograms, *Trans. Am. Oph. Soc.* 2004; 140: 67-74). The nomograms cover a power change range ± 0.5 D to ± 2.0 D in 0.25 D increments. The minimum number of adjusted lenses for each point in the nomograms is ≥ 16 individual LALs.

In response to Dr. McDonald's questions, the irradiated lenses from this study had an average power of +20.0 D. However, due to manufacturing tolerances we typically see a first standard deviation in the power of our molded lenses around ± 0.1 D. The amount of spherical aberration in our lenses over a 4 mm aperture is on the order of about 0.3 to 0.4 diopters. So we have plus or minus 0.05 in our first standard deviation from the spherical aberration term. Dr. McDonald also raises a question about the ability of the patient to maintain fixation during the allotted treatment times (40-120 seconds) and how this would affect the outcomes if submicron accuracy is required. Although the data was not presented in our paper or talk, we have studied this issue. We have videotaped the LAL through a slit lamp camera during patient irradiations and then reduced the data to determine the amplitude and direction of our patient's eye motion. We determined that on average, the patient motion was within 150 microns of alignment 50% of the time and within 230 microns of alignment 90% of the total treatment time. We then programmed a set of motion stages to mimic these saccades in-vitro and irradiated LALs undergoing these movements. Our in-vitro results have shown that this saccadic motion has essentially no impact on the magnitude of power change or the optical quality of our lenses. This can be explained by noting that we use a large beam (> 5 mm) to irradiate our lenses for spherical and cylindrical power adjustments and the individual saccadic excursions tend to average themselves out. And finally, Dr. McDonald brought up a question regarding retinal toxicity and the treatment procedure. We have performed extensive reviews of the literature as well as non-sequential ray tracing simulations to determine the dose of light that would strike the retina. From this work, we have determined that our applied dose of irradiation is an order of magnitude less than that which we would expect to induce any type of retinal lesion.