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Article

Intraocular Photobonding to Enable Accommodating Intraocular Lens Function

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Purpose: Accommodating intraocular lenses (A-IOLs) require capturing the ciliary muscle forces. Prior work demonstrated strong photo-initiated bonding between strips of capsular bag and poly(2-hydroxyethyl methacrylate); (pHEMA) polymer in an extraocular setting. We demonstrate that photobonding can be achieved intraocularly.

Methods: Phacoemulsification was performed in porcine eyes (<24 hours postmortem). A commercial intraocular lens (IOL; pHEMA-MMA material) was inserted in the capsular bag. Surface contact between the lens and capsular bag was ensured by continuous air infusion into the anterior chamber of the eye, which provided sufficient pressure at the interface, as well as oxygen. The capsular bag and IOL then were stained with 0.1% photosensitizer Rose Bengal (RB) solution. A fiberoptic probe connected to a diode-laser (532 nm) was used to locally irradiate the capsular bag–IOL interface intraocularly. The bonding breaking load was evaluated in a uniaxial stretcher.

Results: Photobonding occurred in the 0.8 to 1.6 W/cm^2 irradiance range and 2.5 to 7 minutes irradiation time. Average forces of 0.12 N stretched but did not break the bond. These forces, applied uniaxially, are higher than the summed net accommodating force of the ciliary muscle along the entire equator (0.08 N). In two cases, the zonulae broke before the bonded region.

Conclusions: Photobonding between the capsular bag and IOL polymer can be achieved intraocularly, in a procedure compatible with standard cataract surgery. This technique will enable the mechanisms of A-IOLs not to rely on capsular bag integrity or natural haptic fibrosis.

Translational Relevance: Intraocular photobonding holds promise to enable operation of A-IOLs to restore accommodation in presbyopia, affecting 100% of the population >45 years old. Intraocular bonding of polymer material to ocular tissue also may find other applications in ophthalmology.

Introduction

Photobonding of tissue has been proposed as a method of wound closure in ophthalmology[1] and dermatology[2] applications. In this technique, the sides of the wound are impregnated with a photosensitizer, Rose Bengal (RB), and cross-linked with green light irradiation.

We previously proposed a photobonding method (capsular bag to polymer material) to engage the haptics of an intraocular lens (IOL; after phacoemulsification) to the peripheral region of the capsular bag, as an enabling mechanism for accommodating IOLs (A-IOLs) to operate.[3,4] An efficient intraocular bonding method of tissue to polymer material also may find applications in securing sulcus implanted IOLs[5] (replacing sutures, or cyanoacrylates or fibrin glues, with reported toxicity, short-life, potential for disease transmission or dependent on the coagulation cascade) or preventing leakage in glaucoma shunt surgery.[6,7]

In a previous study we demonstrated RB/green light mediated photobonding (RBPh) of IOL polymer to the crystalline lens capsular bag tissue ex situ.[8] In the former study, strips of New Zealand rabbits were bonded to strips of poly(2-hydroxyethyl methacrylate; pHEMA), using green (532 nm) laser irradiances between 0.25 and 0.65 W/cm^2. The strength of the bonding was tested using uniaxial extensiometry. For fixed fluences, the bonding breakage load increased exponentially with irradiation time from 0.5 to 3.5 g/mm^2, for 30 to 180 seconds of irradiation times (for 0.45 W/cm^2). Photobonding was 1.6 times more efficient in an air than in a nitrogen (oxygen-depleted) environment. These polymer-capsular bag bonding breakage loads were substantially greater than the maximum force of the ciliary muscle, and suggested that this technology may be used successfully to engage A-IOLs to the capsular bag, provided that the paradigm could be translated intraocularly, in a cataract surgery setting.

In the current study, we demonstrated the polymer-capsular bag RB photobonding method intraocularly, reproducing the conditions present in an actual crystalline lens extraction. We achieved strong photobonding forces between an IOL implanted intracapsularly and the peripheral capsular bag, comparable to those obtained previously ex situ, and larger than the net forces of the ciliary muscle.

Methods

Photobonding Light Probe and Photosensitizer

A light probe for intraocular photobonding was developed specifically for this study. The illumination source was a pumped all-solid-state device with 532 nm central wavelength (CNI Tech, Co., LTD, China), which was part of an illumination setup used in earlier studies for cross-linking and ex-situ photobonding.[8,9] The collimating system was bypassed and the fiber tip connected to a 1 mm diameter fiberoptic poly(methyl methacrylate) (PMMA) probe, suitable for insertion through a corneal incision. The experiments were performed at 0.8 and 1.6 W/cm^2 irradiance for 2.5 and 7 minutes.

RB solution (0.1% wt/vol) was used as a photosensitizer. For the preparation, 0.01 g RB (Sigma-Aldrich Corp., St. Louis, MO) were dissolved into 10 mL of a previously prepared 0.01 M phosphate buffered solution (PBS; Sigma-Aldrich Corp.).

Porcine Eye and IOL

A total of 20 freshly enucleated porcine eyes (<24 hours postmortem; 6-month-old animals) were obtained from a local slaughterhouse (Matadero Madrid Norte, Madrid, Spain), kept at 4°C, and used for trials and pilot studies. Four eyes were used in the final essays reported here. All eyes were obtained according to the European guidelines for animal experimentation.

Commercial monofocal equi-biconvex IOLs (Akreos MI60 IOL; Bausch & Lomb, Rochester, NY) were used for implantation. The material for the IOL and haptics is a copolymer of pHEMA and methyl methacrylate (MMA). The lens has a one-piece design with four angulated (10°) haptics.

Intraocular Surgery

The eyes were placed in a holder under a desktop operating microscope (Carl Zeiss Meditec AG, Jena, Germany). The procedure, involving eye preparation, phacoemulsification and IOL implantation, photobonding, and mechanical testing, is illustrated in Figures 1 and 2 and Supplementary Videos S1 to S3.

Before intraocular surgery, a flap was performed in the sclera (Figs. 1A, 1B). This flap was used after the photobonding procedure to clamp the sclera to the stretcher to evaluate the bonding forces.

According to standard cataract surgery practices, a main incision (2.2 mm; Fig. 1C) was performed, followed by direct phacoemulsification (Laureate World Phaco System; Alcon Laboratories, Ft. Worth, TX; Fig. 1D), without a prior capsulorhexis. The final stages of the aspiration were performed with the irrigation/aspiration tip to reduce the risk of posterior capsule rupture. Before removing the phaco (or I/A) tip, two auxiliary incisions perpendicular to the main incision were performed, one for an anterior chamber maintainer and one for the laser probe. During the rest of the surgery, air was constantly infused through the anterior chamber maintainer to pressurize the anterior chamber. The IOL was introduced through the main incision (Fig. 1E) and placed inside the capsular bag.

RB solution (0.1 mL) was injected using a 1 mL syringe and a 27G cannula (Fig. 1F). The RB solution was left in the capsular bag for 2 minutes to achieve staining of the capsular bag tissue and IOL. Excess RB was removed through aspiration while pressing the anterior capsule against the IOL with air infusion.

The laser probe was introduced through the remaining auxiliary incision and aimed with a 30° inclination towards the capsule–IOL to be bonded (Fig. 1G). The air pressure facilitated the surface

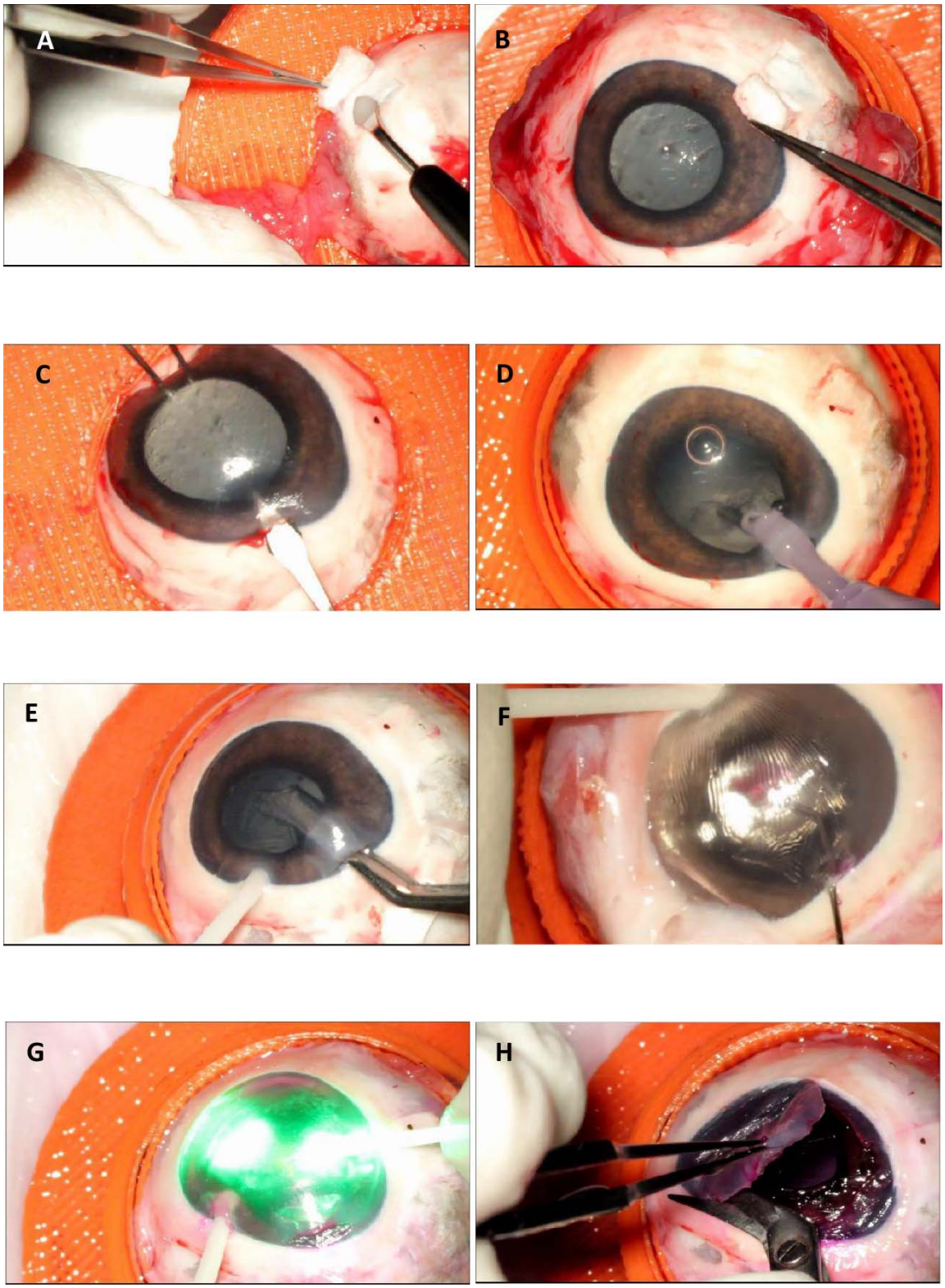

Figure 1. Steps of the surgery and photobonding. (A, B) Flap cut, back and front views. (C) Performance of the main incision. (D) Phacoemulsification. (E) Insertion of the IOL while infusing air through the anterior chamber maintainer. (F) RB insertion. (G) Green light irradiation with a probe. (H) Cut of the cornea after irradiation. The complete intraocular photobonding procedure can be seen in Supplementary Videos S1 to S3.

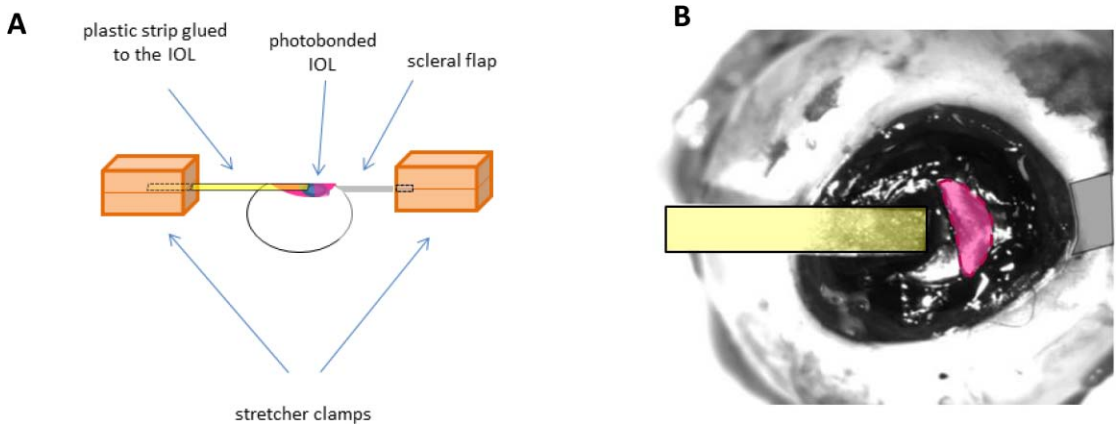

Figure 2. (A) Set up of the stretcher with the sample mounted. (B) Photograph of the plastic strip (*yellow*) glued to the photobonded IOL (*pink*). The scleral flap (*gray*) and plastic strip are clamped to the stretcher.

contact between the IOL and capsular bag during irradiation, and also provided oxygen to the photochemical reaction. The illuminated area was approximately 6 mm^2 and the probe was at a 3 mm distance from the bonding surface.

A total of 4 implants and photobonding conditions are reported. The implantation protocols and photobonded area were similar in all cases, while irradiance was varied between 0.8 and 1.6 W/cm^2, and irradiance time between 2.5 and 7 minutes.

Uniaxial Stretching

To evaluate the result of the intraocular photobonding process, the cornea was removed after irradiation (Fig. 1H) and a 2.5 × 0.5 cm piece of plastic was glued to the IOL. The sample was mounted in a commercial uniaxial stretcher (USstretch; Cellscale, Waterloo, ON, Canada), as seen in Figure 2. The plastic rod was clamped to one arm of the uniaxial stretcher and the scleral flap was clamped to the other arm. The free length of the sample between the clamps was 30 mm before stretch.

Within each stretching cycle, the clamps were first progressively separated (stretching period), and then progressively returned to the initial position (relaxation period), while the force was recorded continuously. The position of maximum displacement, defined the amplitude of the stretching–relaxation cycle, was increased in successive cycles for the same sample. We applied cycles of 3, 4, 4.5, 5, and 6 mm displacement. Besides, one of the eyes underwent a complete stretching until full tissue breakage and separation.

For each stretching–relaxation cycle, the stretching force was plotted versus the displacement during stretching or relaxation of the sample. The highest applied bonding force corresponded to the maximum of that curve, while the tissue breaking force corresponded to the force at which there was an abrupt decrease in the force during stretching.

After the stretching–relaxation cycles, the samples were examined under the microscope to assess the integrity of the 6 mm^2 bonded region: whether the capsule was stained, creased, broken, teared, or separated from the IOL.

Transmittance of RB-Stained Capsular Bag and IOL

As a first estimation of the RB staining of the samples, a power meter was used to calculate the transmittance of the stained capsular bag and IOL. The stained and bonded regions were placed between the laser and power meter, and the drop in measured power through the sample was measured.

Control Sample

As a control, a similar procedure was conducted with all steps identical to the tests described above (including capsular bag and IOL stained with 0.1% RB solution and left for 7 minutes), but without laser irradiation. The IOL and capsular bag detached before being mounted in the stretcher. This demonstrated that photobonding requires green light photoactivation to occur.

Results

Intraocular IOL-Capsular Bonding

Visual exploration of the sample under the microscope before the stretching procedure showed

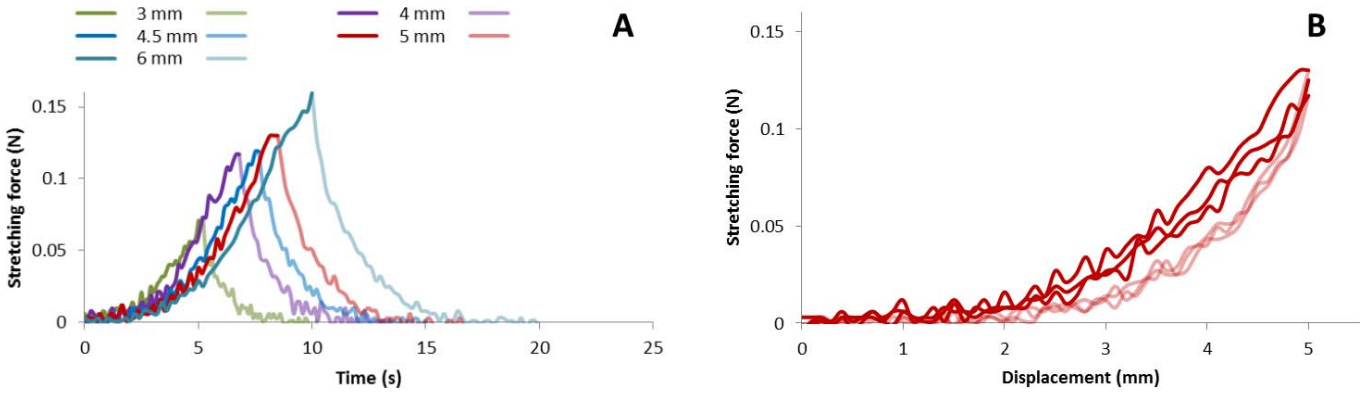

Figure 3. (A) 3, 4, 4.5, 5, and 6 mm stretching cycles of the photobonded sample irradiated at 1.6 W/cm^2 for 2.5 minutes. *Dark line* corresponds to the stretching period and the *light line* corresponds to the relaxation period of the cycle. (B) 5 mm stretching–relaxation cycle (three consecutive repetitions).

that the anterior capsular bag was firmly photobonded to the IOL in all samples. There were no capsular bag creases on the photobonded area, which covered an approximate extension of 6 mm^2.

RB capsular bag filling produced uniform staining of the capsular bag and IOL. The transmittance of the stained capsular bag was measured at 33%. Staining also was observed in the zonulae. Therefore, the transmitted irradiance through the stained IOL and capsule was in the 0.26 to 0.53 W/cm^2 range.

Bonding Forces

Figure 3A shows the consecutive stretching–relaxation cycles of samples irradiated at 1.6 W/cm^2 for 2.5 minutes. Cycles of 3, 4, 4.5, 5, and 6 mm were performed to assess the forces that the bonding could hold at displacements higher than those occurring during natural accommodation. The stretching–relaxation cycles have been represented as a function of time to be able to see all cycles. Therefore, the graphs have been normalized to time. The data indicated that the stretching force increased with the cycle displacement, since the photobonded area was supporting higher forces. After the relaxation period, at the end of the cycle, the force was lower than 0. We attribute this to small detachments of the scleral flap during the cycle. The photobonded area remained intact during the cycles.

The 5 mm stretching–relaxation cycle was repeated three times (Fig. 3B). The graph shows a high repeatability in the transmission of the force, with some asymmetry in the stretching and relaxation periods. In particular, the maximum stretching force did not significantly decrease in the successive cycles. A small decrease is attributed to microdetachments in the scleral flap during the stretching period.

Figures 4A to 4D show the last stretching–relaxation cycle measured for each sample. The stretching force is plotted for each displacement for the stretching (dark line) and relaxation (light line) periods. Data correspond to different irradiation protocols. Samples A and B were irradiated for 2.5 minutes; samples C and D were irradiated for 7 minutes. The irradiance was 0.8 W/cm^2 for samples A and C (left graphs) and 1.6 W/cm^2 for B and D (right). The amplitude of the stretching cycle (dashed line), was 6 mm in samples A and B, 5 mm in sample C, and 10 mm in sample D. The stretching–relaxation cycle depicted in sample B was measured after performing the three stretching–relaxation cycles shown in Figure 3B.

In samples A and B (Fig. 4), there was a steady increase in the stretching force before the maximum achieved displacement. The force was roughly symmetric around the maximum, with a steeper slope in the relaxation than in the stretching periods. However, samples C and D show a discontinuity downwards before the end of the stretching cycle, anticipated by a short period of stable force. This drop in the force was not associated with breakage of the bonding between the IOL and capsular bag, but rather to a breakage/detachment of the zonulae or other tissues, since the capsule–IOL bond was intact after stretching.

The maximum recorded forces ranged between 0.10 (sample C) and 0.16 N (sample B), which should be understood as a lower bound of the bonding force. The tissue breakage force was estimated to be 0.10 and 0.12 in samples C and D, and higher than 0.11 and 0.16 in samples A and B. The measured forces per photobonded area ranged from 0.017 to 0.027 N/

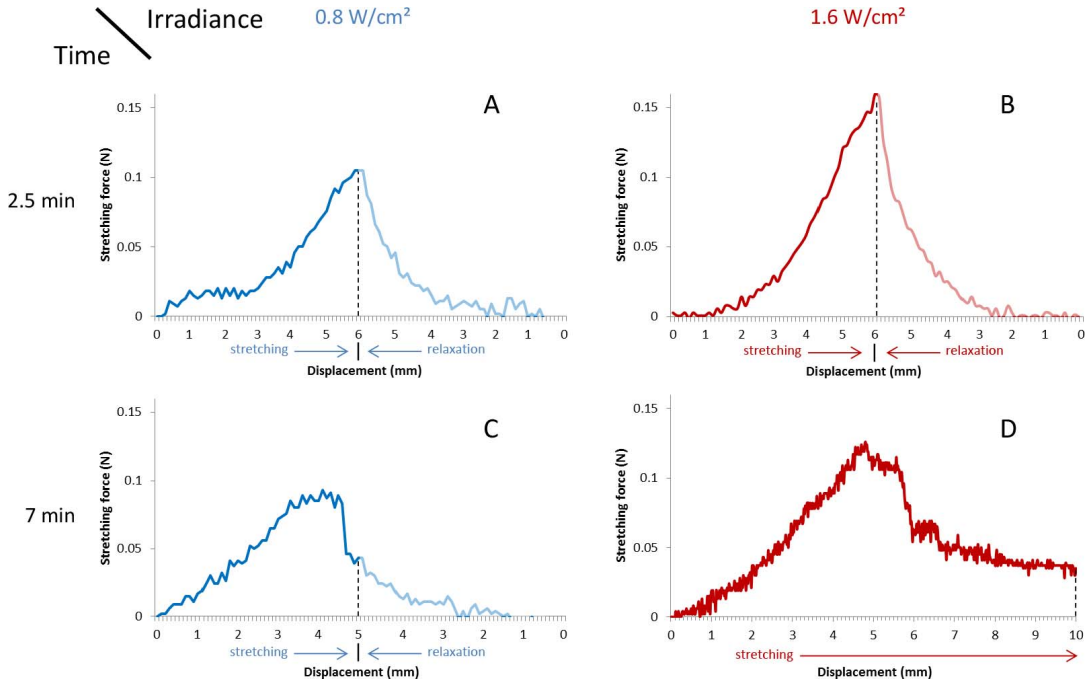

Figure 4. Stretching–relaxation cycles of the photobonded samples irradiated with different irradiances and times. The Figure shows the last stretching cycle of each sample. Samples A and B have symmetric and continuous response around the maximum force, coincident with the maximum displacement. In samples C and D, there is an abrupt force decrease that occurs before the maximum stretching distance, consistent with a tissue breakage. See text for details.

mm^2. The results in Figure 4 are consistent with a weakening of the tissue with longer irradiation times (7 versus 2 minutes), but do not provide information about the influence of irradiation conditions on the strength of the bonding between the IOL and capsular bag.

For all the samples, the measured uniaxial bonding force was higher than 0.08 N, which is the sum net force of the ciliary muscle excerpted along the equator of the human eye during accommodation.[10] In the control sample, we could not measure any force, since the IOL was not bonded to the capsular bag.

Discussion

Engagement of the haptics with the capsular bag is essential in the operation of prospective A-IOLs, allowing transmitting the forces of the ciliary muscle into the lens. Some A-IOLs, such as the Crystalens (Bausch & Lomb),[11] are expected to operate by axial shift, with the haptics of the A-IOL being engaged to the capsular bag by unpredictable natural fibrosis processes. Other concepts, such as the Zonular Capture Haptics, also acknowledge the limitations of designs that rely on the integrity of the capsular bag to mold the shape or displace one or more elements of the A-IOL, and propose haptics that promote fusion of the anterior and posterior surfaces of the capsular bag, so that they remain securely sealed and captured within the capsular bag.[12] Still, this system requires a natural or assisted process of fibrosis, and is generally conceived to be deployed in a two-step surgical process where an optical platform with haptics is implanted, and in a second step, the lens (a rigid single or double axially-moving optics, or a flexible lens changing its curvature) is implanted.

We presented a method that can be used to bond IOLs to the capsular bag, allowing an immediate strong bonding (not relying on natural fibrosis), and able to transmit the accommodative forces to the IOL, using a photoactivated procedure. We demonstrated that the method is compliant with a standard cataract surgery, and have implemented the surgical steps that are specific to the newly developed method and its test: the position and size of the incisions to insert the laser probe for irradiation, the photoinitation (RB) capsular bag staining, the air infusion strategy to facilitate surface contact and photochemical reaction, and its deployment as an anterior chamber maintainer. Additionally, and only for experimental quantification of the bonding, a scleral flap was performed to uniaxially stretch the sample

after photobonding, to measure the stretching force that the bonding can resist before detachment of the zonulae. We considered avoiding the use of viscoelastic during the surgery to prevent retention of viscoelastic material between the capsular bag and IOL, which may compromise the photobonding reaction. Also, there is evidence that complete filling of the anterior chamber with air is safe in endothelial transplant surgeries.[13]

Postoperatively, we demonstrated that a strong bond was created between the capsular bag and IOL. The measured force that the photobonded IOL–capsular bag can transmit (0.12 N on average in our experiments) was higher than the maximum net accommodating force of the ciliary muscle (0.08 N)[10] and was limited by the resistance of the tissue, not by the bonding resistance itself (Figs. 4A–D).

We also showed that, provided there is no tissue breakage, the bonding can resist repeated stretching cycles (Fig. 3B) with the same force transmission. The maximum measured force broke the zonulae in two cases, and left it intact in two others. The capsular bag–IOL bond supported the stretching forces in all cases, showing that the bonding can resist several stretching–relaxation cycles.

The potential limitation of the method in its current clinical deployment may come from the safety of RB introduced in the anterior chamber. Previous literature has shown that filling of the capsular bag with RB 0.01% does not entail toxicity or endothelial cell loss.[14] While the oxygen-mediated interaction of RB with visible light leads to reactive oxygen species generation, it is unlikely that they reach the corneal endothelium given their relatively short diffusion pathways (microns). On the other hand, the presence of high levels of free radical scavengers in the ciliary processes and aqueous humor would favor the inhibition of singlet oxygen around the photobonded area.[15]

Further refinement of the technique will involve localization of the RB in the polymer surface, in the specific locations to be bonded. In vivo implementation of the technique also should consider light exposure safety aspects. Green laser irradiation is used in retinal surgery with comparable irradiances. In the reported application, light exposure occurs only in peripheral regions of the lens, with minimal retinal exposure. In a previous study of capsular bag-pHEMA bonding ex situ, we found that the largest laser irradiances used produced an increase in brittleness of the capsular bag, which tended to break before the bonded area. While we did not find that the intraocularly applied photobonding compromised the capsular bag, and the current method does not depend on the integrity or flexibility of the capsular bag, the most effective time-irradiance dosage should be selected for the surgical method. An alternative to the current laser probe illumination approach can be achieved by controlled light release only in the regions to be bonded, for example using a fiberoptic ring leaking light in specific locations. In any case, our data suggested that transmittance of light through the stained polymer lens and capsular bag is small (33%); therefore, resulting in low irradiation of the zonulae and ciliary body in the vicinity of the bonded area. While increased zonular weakness has been reported in some cases following laser peripheral iridotomy[16] using green lasers, it should be noted that the effective laser irradiance in the reported photobonding technique is significantly lower.

Another concern is the resistance of the bonding throughout time. Our study of pHEMA-capsular bag bonding ex situ showed that bonding forces persist unchanged for at least 2 years (duration of the experiment) in immersion long term.[8]

Further studies should involve implantation and photobonding in an in vivo animal model, and, following appropriate safety studies, eventually in humans. The current study paves the way towards the achievement, in one surgical step, of bonding between IOL materials and the capsular bag so they can move jointly. This surgery opens the door to the use of newly designed IOLs that will deform with the action of the ciliary muscle similarly to the mechanism of action of the natural crystalline lens.

Comparison Photobonding Ex Situ (Prior Paper) and In Situ

Marcos et al.[8] showed, in an earlier work, photobonding of pHEMA material and porcine capsular bag ex situ (in air). The breaking force was dose- (time and irradiance) dependent, also largely exceeding the reported radial forces of the ciliary muscle. Attempts for intraocular bonding in porcine eye models in that study were successful, but depicted conditions that were not representative of a real surgery; in particular, bonding without excising the cornea (which exposed the capsular bag to air, and allowed flood light exposure into the eye) or creating a scleral window (through which a light probe was inserted). Here, intraocular photobonding is performed on an intact eye, similarly to an actual cataract surgery. Light was

delivered through a 1 mm fiberoptic probe at the interphase between the IOL and the capsular bag.

The measured bonding forces (0.017 to 0.027 N/mm^2) in our study are of the same order of magnitude than those obtained by Marcos et al.[8] ex situ (0.013 to 0.038 N/mm^2, for comparable conditions). Also, measurements in air and in a nitrogen environment revealed that the presence of oxygen increased the bonding efficiency by a factor of 1.63. In the current setting, the surgical protocol involves infusion of air with the triple purpose of favoring the photochemical reaction, producing strong contact of the IOL and capsular bag and being an anterior chamber maintainer. The infusion of air is a common practice in several ocular surgeries, such as vitroretinal surgery, or more closely, to prevent surge and avoid anterior chamber destabilization in bimanual phacoemulsification.

Towards In Vivo Photobonding

While we demonstrated intraocular photobonding using protocols consistent with a cataract surgery procedure, several steps should be replaced by alternatives that are less invasive and more compliant with the final application.

In the current demonstration, parts of the lens were photobonded to the anterior capsular bag. In the final application, larger form-factor haptics will allow conformity to the equatorial regions of the anterior and posterior capsular bag to the outer part of the haptics. Reaching the capsular bag region will require alternative light probes, for example with a flexible tip, instead of the rigid probe used in the current study. Technology is available in the form of ophthalmic endoscopes that incorporate light guides and visualization capabilities to areas that may be obstructed by the iris. Alternatively, light could be directly delivered into the IOL's haptics.[3] The use of visible light (532 nm) results in lower phototoxicity risks in the ocular structures than ultraviolet light (frequently used in photoactivated processes, such as corneal cross-linking). Our results also suggested that the light dose (irradiance and irradiation times) could be reduced to avoid phototoxicity. Besides, the peripheral illumination (equatorial region of the capsular bag) minimizes the risk of retinal exposure, particularly if illumination strategies are optimized. Anyway, potential effects of visible illumination and safe light levels exposures to the zonulae and ciliary processes should be considered.

In addition, full staining of the capsular bag, as performed in the current demonstration, is unnecessary and not suitable in applications in vivo. RB could, in fact, be locally restricted to the outer part of the haptics and achieved by either controlled local release or haptic coating, largely minimizing any potential toxicity of the photoinitiator. Small concentrations of RB (0.01% wt/vol) in stained capsular bags in vivo in a rabbit eye model were, in fact, shown to prevent posterior capsular opacification while not causing undesired antimetabolic effects in adjacent tissues.[14]

Bonding polymers to intraocular tissues through the use of a photosensitizer and light instead of mechanical techniques can lead to a great improvement in surgical approaches to presbyopia correction, IOL instability, or aphakia. This approach could replace the use of synthetic or fibrin glues in sulcus-implanted IOL or in glaucoma shunt surgery.[6,7]

A firm engagement of the A-IOL haptics to the capsular bag's peripheral region will allow transmission of the ciliary muscle forces to the lens optics, and, therefore, functional accommodation. The demonstration of intraocular bonding of IOL materials represents a proof-of-concept for a new paradigm for A-IOLs, and, therefore, a first step towards translation.

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*NA-A and RG-C have equally contributed to this work.

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Supplementary Material

Supplementary Video S1. Intraocular photobonding.

Supplementary Video S2. Sample preparation.

Supplementary Video S3. Stretching.