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SURGICAL INTERVENTION AND ACCOMMODATIVE RESPONSES: I. CENTRIPETAL CILIARY BODY, CAPSULE AND LENS MOVEMENT IN RHESUS MONKEYS OF VARYING AGE

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Abstract

Purpose—To determine how surgically altering the normal relationship between the lens and the ciliary body in rhesus monkeys affects centripetal ciliary body and lens movement.

Methods—In 18 rhesus monkey eyes (aged 6–27 years), accommodation was induced before and after surgery by electrical stimulation of the Edinger-Westphal (E–W) nucleus. Accommodative amplitude was measured by coincidence refractometry. Goniovideography was performed before and after intra- and extra-capsular lens extraction (ICLE, ECLE) and anterior regional zonulolysis. Centripetal lens/capsule movements, centripetal ciliary process (CP) movements, and circumlental space were measured by computerized image analysis of the goniovideography images.

Results—Centripetal accommodative CP and capsule movement increased in velocity and amplitude post-ECLE compared to pre-ECLE regardless of age (n=5). The presence of the lens substance retarded capsule movement by ~21% in the young eyes and by ~62% in the older eyes. Post-ICLE compared to pre-ICLE centripetal accommodative CP movement was dampened in all eyes in which the anterior vitreous was disturbed (n=7), but not in eyes in which the anterior vitreous was left intact (n=2). Following anterior regional zonulolysis (n=4), lens position shifted toward the lysed quadrant during accommodation.

Conclusions—The presence of the lens substance, capsule zonular attachments, and Wiegert ligament may play a role in centripetal CP movement. The capsule is still capable of centripetal movement in the older eye (although at a reduced capacity) and may have the ability to produce ~6 diopters of accommodation in the presence of a normal young crystalline lens or a similar surrogate.

INTRODUCTION

Presbyopia (the loss of accommodation with age) has been attributed to increased hardness of the lens,^{1–7} lens growth,^{6, 8–14} and loss of elasticity of the ciliary muscle's posterior attachments.^{15, 16} No individual over the age of 45 years appears exempt, making presbyopia the most common ocular affliction in the world. Although certainly not a blinding condition,

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and correctable by various optical means, presbyopia's cost in devices and lost productivity is substantial.

Since the accommodative apparatus of the rhesus monkey is similar to that of the human,^{17–19} and both species develop presbyopia on a similar timescale relative to lifespan^{19–21} experimental studies elucidating the role of the various structures for development of presbyopia can be performed in the rhesus. In addition, this study for the first time characterizes the function of the eye's various accommodative components following lens extraction procedures, which are undertaken in millions of human patients every year (either unilaterally, bilaterally at separate time points, or in some cases bilaterally during the same surgery day). The information generated from these studies is critical to the successful development of an accommodating intraocular lens (IOL).

We determined how surgically altering the normal relationship between the lens and the ciliary body in live rhesus monkeys 6–27 years of age affects the normal centripetal movements of the ciliary body and lens/capsule.

MATERIALS AND METHODS

Details of all equipment and animal handling procedures for anesthesia, iridectomy, electrode implantation, central stimulation, measurement of accommodation, image calibration, goniovideography, velocity²² measurements, etc. have been described previously.^{20, 23–26} All procedures conformed to the ARVO Statement for the Use of Animals in Research and were in accordance with institutionally approved animal protocols.

Monkeys

Twenty-five rhesus monkeys (*Macaca mulatta*) of either sex, aged 6–27 yr and weighing 5.0–13.4 kg, were studied. The monkeys all had normal phakic eyes with no signs of ocular pathology (other than age-related lenticular opacification), as assessed by slitlamp examination. Animals were evaluated for corneal clarity and anterior chamber and anterior vitreous inflammatory reaction before and after surgery.

Eight of the monkeys, aged 17–26 yr and weighing between 7.2 kg and 9.5 kg, were designated solely for measurements used in the calculation of the normal velocity of the ciliary process (CP) and lens centripetal movements during accommodation and disaccommodation at supramaximal central stimulation.

The remaining 17 monkeys underwent surgical procedures. Baseline measurements of the normal accommodative response in the eyes of each animal were taken before the surgical procedures were performed. Three lens surgery procedures were used in the study: intracapsular lens extraction (ICLE); extracapsular lens extraction (ECLE); and anterior regional zonulolysis (ARZ). (See Surgical Procedures, below.)

From the 17 monkeys designated for surgery, 18 eyes underwent successful surgical procedures, as described below. These 18 eyes were divided into 2 groups, according to age, to allow comparisons of young (6–13 yr) versus older (17–27 yr) eyes (Table 1). The 2 age groups were then further subdivided into 3 groups, each comprised of both young and older monkeys, according to which surgical procedure they received (see Table 1). No surgical group had two eyes from the same monkey.

Ten monkeys (5 young; 5 older) each provided one eye for surgical intervention (ICLE, n=4; ECLE, n=2; ARZ, n=4); the opposite eye was iridectomized but otherwise surgically untouched and served as a contralateral control eye for morphological examination.

One additional young monkey also provided one eye for the ICLE procedure (ICLE, n=1), with its opposite eye iridectomized but otherwise surgically untouched; however, this monkey was not euthanized and was retained for another study. Therefore this eye did not undergo morphological examination. Another older monkey contributed 1 eye to the ICLE group and, in a subsequent surgery, contributed the opposite eye to the ECLE group. Surgery in this monkey's second eye was allowed by the veterinary staff of our institution and the Institutional Animal Care and Use Committee, since the surgery was carried out at a separate time point from the first eye and cognitive behavior was observed by laboratory personnel and veterinary staff to ensure that the animal was functioning normally before and after surgery. If signs of visual or other distress had been observed, the animal would have been euthanized. However, no overt signs of distress were noted in any animal. Both of these eyes underwent morphological examination.

In each of the 5 remaining monkeys (n=3 young; n=2 older), surgical procedures were performed initially in one eye (ICLE, n=3; ECLE, n=2). However, the post-surgical clinical examination of these 5 eyes uncovered surgical or technical complications that likely would have impacted the accommodative apparatus in ways not intended by the surgery protocols, which were designed to disrupt specific parts of the accommodative apparatus. These complications were: ciliary body degeneration (n=2, ICLE); severing of the posterior zonular attachments (n=1, ICLE); and perforation of the posterior capsule, capsular fibrosis and lens cell regrowth with pronounced presence of pearls and Soemmering's ring (n=2, ECLE). Therefore the decision was made, before post-surgical imaging, not to include post-surgical imaging data for these 5 eyes in the study. Subsequently, in each of these 5 monkeys the contralateral eye also underwent surgery (ICLE, n=3; ECLE, n=2). These eyes were free of post-surgical complications, based on clinical examination, and the post-surgical imaging of these eyes was completed according to protocol. Again, cognitive behavior was observed for overt signs of distress following surgery in the second eye. However, the animals' function in their cage environment appeared normal. For the older animals, the loss in accommodative ability (through either ECLE or ICLE) was not really a change since most, if not all, of their ability to accommodate had already been lost. For the younger animals, this meant an adjustment to the presbyopic condition at an earlier age. These eyes (young and older), being aphakic after surgery, lost distance acuity as well. However, because the monkeys were housed in a room within the animal care facility their visual space and need for far distance vision was limited accordingly, and thus any aftereffects on the monkeys by this surgically induced loss of distance vision were reduced. The second eye for surgery did not appear to adversely affect the monkey's ability to function normally within the caged environment, as determined by daily observation by both laboratory and veterinary staff.

The strategy of using the second eye in these monkeys, under the careful constraints indicated, avoided major intracranial surgery in additional monkeys. All of the eyes included in the study underwent morphological examination.

In summary, a total of 26 eyes from 25 monkeys were used in the study: 8 eyes were used solely for measurements used in calculating normal CP velocity and lens centripetal movements; 18 eyes from the remaining 17 monkeys underwent successful surgical procedures: ICLE, (n=9 monkey eyes; 5 young, 4 older); ECLE (n=5 monkey eyes; 3 young, 2 older); and ARZ (n=4 monkey eyes; 1 young, 3 older).

Surgical Procedures

Intracapsular lens extraction (ICLE)—ICLE, entailing removal of the entire lens and capsule, was performed by the standard clinical technique in 9 monkey eyes. Following a fornix-based conjunctival flap, and a 150° corneoscleral limbal groove, the anterior chamber was entered, the incision was extended within the groove for the full 150°, the zonule was lysed

with α -chymotrypsin (83 units/ml, Sigma, St. Louis, MO) injected into the anterior chamber, and the lens and capsule were removed intact with a cryoprobe. In 7 (3 young, 4 older) of the monkey eyes undergoing ICLE, the α -chymotrypsin was allowed to remain in the anterior chamber for 1–2 minutes before rinsing and removal of the lens. Mechanical anterior vitrectomy (Ocutome) and toileting of the wound were performed as needed, and the wound was closed with interrupted sutures of 9/0 or 10/0 nylon. In the remaining 2 monkey eyes (both young) in this group, the α -chymotrypsin was allowed to remain in the eye for <30 seconds before fluid rinsing and removal of the lens with a cryoprobe. Wieger's ligament remained intact in these 2 young eyes post-ICLE, and mechanical vitrectomy was not required.

Extracapsular lens extraction (ECLE)—ECLE, entailing removal of the lens substance from within the capsule, leaving an empty capsule bag still attached to the zonula, was performed in 5 monkey eyes (3 young; 2 older). The standard clinical ECLE technique was used, involving a fornix-based conjunctival flap; intracameral instillation of viscoelastic; large anterior capsulotomy (~4 mm); irrigation/aspiration $\pm$ phacoemulsification with an Alcon (series 20,000 Legacy Model #STTL Phaco) unit; removal of viscoelastic; and wound closure.

Regional zonulolysis of the anterior zonule (ARZ)—In 4 monkey eyes (1 young, 3 older), two μ l of 40 units/ml of α -chymotrypsin were dissolved in heavy sucrose medium (10% sucrose solution) and injected into the anterior chamber near the anterior zonular fibers, to regionally dissolve 1–2 clock hours of the anterior zonule²⁷ (“anterior zonular fibers” in this manuscript refers to the fibers that course to the anterior, posterior and equatorial lens surfaces). The head of the monkey was oriented so that the heavy solution fell with gravity to the lens/anterior zonule/muscle interface (see Video clip #1) in either the nasal (n=3 eyes) or temporal (n=1 eye) quadrant. The end of the needle was visualized so that when the injection was made, the solution was seen falling onto the anterior zonular fibers.

Accommodation, Stimulation, and Response Measurements

Refractometry—A Hartinger coincidence refractometer (Jena, Germany) was used to measure resting refractive error and accommodation in response to electrical stimulation of the Edinger-Westphal (E–W) nucleus. Accommodation was stimulated centrally via the implanted electrode. Supramaximal stimulus settings were chosen (as defined below) that induced maximum accommodative responses (i.e., maximum centripetal CP and lens/capsule movement, maximum forward ciliary body movement) and maximum accommodation, allowing comparisons to be made between pre- and post-surgical accommodative responses. The forward ciliary body movements are beyond the scope of this paper and will be reported elsewhere. [IOVS #0002]

Maximum accommodative amplitude was induced, measured, and tabulated for each monkey eye during 4 to 5 separate experimental sessions prior to surgery.

Maximal stimulus is defined as the level of E–W stimulus current necessary to induce maximum accommodative change, measured refractometrically. *Supramaximal stimulus* is a level of E–W stimulus current ~25% (or ~0.10 to 0.20 mA) above the maximal stimulus that ensures maximum centripetal CP and lens movement. *Circumlental space* is the average distance from the tips of 4–5 ciliary processes to the equatorial edge of the lens or capsule as measured in the goniovideography images²³ in both the nasal and temporal quadrants (two separate locations 180 degrees from each other).

Comparisons of circumlental space were made at rest, at maximal stimulation, and at supramaximal stimulation pre- and post-ECLE. All other pre- and post-surgical comparisons were made at rest vs. supramaximal stimulation.

Goniovideography Imaging—Dynamic goniovideography images (using a Swan-Jacobs gonioscopy lens) were obtained during stimulation of accommodation and then recorded to videotape (30 frames per second).²⁰ Goniovideography²⁰ was performed before and after each surgical procedure. The post-surgery imaging sessions were carried out 2.5 weeks to 3 months after surgery. Measurements were taken at the beginning of the study in all 25 monkeys, using goniovideography, to enable calculation of the normal velocity²² of the CP and lens centripetal movements at supramaximal stimulation. In the 18 monkey eyes that underwent surgical procedures, goniovideography allowed measurement of the centripetal lens/capsule and CP movement (i.e., velocity²² and amplitude²⁰) and measurement of the circumlental space width²³ before and after surgical intervention.

Computerized analysis of the goniovideography images was used to measure the extent and dynamics of the centripetal lens and CP movements during accommodation and disaccommodation in both the nasal and temporal quadrants (180 degrees from each other) and an average value calculated for each eye.²⁰ The mean $\pm$ s.e.m. dynamic centripetal movements of the capsule edge or lens equator (if present) and 4–5 adjacent ciliary processes during 2.2 second-long stimuli were plotted.

Histology

The animals were perfusion-fixed through the heart with 4% paraformaldehyde, after perfusion with one liter of 0.1 molar PBS (phosphate buffered saline). After enucleation, slits were cut in the posterior sclera and a window cut in the anterior cornea to enhance fixative penetration and preserve the architecture of the ciliary muscle and its posterior attachment to Bruch's membrane. The eyes were then immersed in Ito's fixative²⁸ until they were sent to Erlangen, Germany for morphological investigation. Small sectors of the anterior globe, including the entire ciliary body and adjacent cornea and sclera, were embedded in Epon, and 1 μ m semithin sections were cut and stained with Richardson's stain.²⁹

Statistical Analysis

Average CP and lens movement amplitudes were calculated for 2 quadrants (nasal and temporal) of each eye at each time point (1/30th of a second) during stimulation. The mean $\pm$ s.e.m. centripetal CP and lens movement amplitudes were calculated by using the movement amplitude from 20 consecutive frames, beginning 25 frames before termination of the stimulus (i.e., when the eye was in the stable accommodated state). The initial velocity of CP and lens or capsule movements was determined by the movement amplitude change from 5 frames to 15 frames after the beginning of the stimulus. Disaccommodative velocity was measured between 5 frames to 13 frames after the stimulus was discontinued. The area under the entire stimulus response curve of CP and lens or capsule movement was also calculated. The response curve included the 2.2-second stimulus duration plus the time during which the ciliary processes or lens/capsule returned to baseline position. Comparisons were made between pre- and post-surgery velocity, amplitude and area under the curve for both lens and CP movement.

A two-tailed paired t-test was used to detect significant differences. A p-value ≤ 0.05 was considered significant; $0.05 \leq p \leq 0.10$ was considered to indicate a trend, given the small number of monkeys.

RESULTS

To give an indication of the range in accommodative amplitudes and variability within each eye for each group, the mean $\pm$ s.e.m. accommodative amplitude was calculated for all pre-surgical experimental sessions within each monkey eye. The resulting mean values for each of the young monkey eyes ranged from 16.4 ± 1.5 diopters to 18.2 ± 0.2 diopters, while the

resulting mean values for each of the older monkey eyes ranged from 0.9 ± 0.1 diopters to 6.9 ± 0.5 diopters.

Centripetal Ciliary Process (CP) Movement as Measured by Goniovideography

During accommodation and disaccommodation, the velocity of the older lens was less than in the young eyes (accommodation, $p=0.034$; disaccommodation, $p=0.082$; Table 2). In contrast, the velocity of the ciliary processes during the same period was similar in the young and older eyes.

Intracapsular Lens Extraction (ICLE)—Post-ICLE, CP movement depended on whether the anterior vitreous (i.e., Wieger's ligament) was intact or not. In the eyes in which α -chymotrypsin stayed for < 30 sec and no vitrectomy was performed, Wieger's ligament was intact. In these eyes we also observed zonular attachments between Wieger's ligament and the ciliary processes (Fig. 1, Video Clip #2). Eyes were grouped according to whether Wieger's ligament was disrupted (ICLE+WD) or intact (ICLE+WI), for the sake of comparison.

a) ICLE+WI (Intracapsular Lens Extraction + Intact Wieger's Ligament and Zonular Attachments between the Ciliary Processes and Wieger's Ligament): The entire lens and capsule were removed from 1 eye of each of 2 young monkeys in the ICLE group, leaving Wieger's ligament intact (Fig. 1). (Croft MA, et al. IOVS 2004;45:ARVO E-Abstract 2187) The presence of Wieger's ligament and the zonular arrangement (shown in Video Clip #2, Fig. 1) was confirmed by a vitreo-retinal specialist (Michael Nork, MD) and a cataract surgeon (Gregg Heatley, MD) by slitlamp examination. Further, the Wieger's ligament structure seen in Figure 1 and Video Clip #2 has a smooth edge and cannot be the edge of a torn capsule remnant, as that would appear ragged rather than smooth. Wieger's ligament appeared to move centripetally in accordance with the CP accommodative response, and the zonular fibers appeared to relax (see Video Clip #2). Following ICLE+WI (Fig. 2), the initial CP velocity was similar to baseline (Table 2, Fig. 2) but the area under the CP movement curve, and the amplitude of CP movement that was achieved near the end of the stimulus train, was greater following ICLE+WI (Table 3, Fig. 2) than at baseline before lens removal but the difference was not statistically significant given the small sample size.

b) ICLE+WD (Intracapsular Lens Extraction + Disruption of Wieger's ligament): In the 3 other young monkeys, and the 4 older monkeys that underwent ICLE, the entire lens and capsule were removed from 1 eye and Wieger's ligament was disrupted (Fig. 3). Following ICLE+WD, CP velocity declined significantly, while CP movement amplitude, and the area under the CP movement curve tended to decline (Table 3) compared to the same eyes pre-surgically, regardless of age (Fig.3, Table 2).

Extracapsular Lens Extraction (ECLE)—In all 5 monkey eyes (3 young, 2 older) that underwent ECLE, the lens substance was removed from the capsule, leaving an empty capsule bag (ciliary processes, zonules, and posterior capsule left intact; Fig. 4).

At the time of post-surgical imaging, the eyes were examined for pearls, adhesions, and any age-related differences. In the young eyes, the empty capsular bags did not have folds and appeared smooth and semi-transparent, with no evidence of pearls or of anterior-posterior capsule adhesions (Fig. 4A compared to 4B; Video Clip #3). In the older eyes, the empty capsule bags had several folds but also appeared semi-transparent, and without evidence of pearls or of anterior-posterior capsule adhesions (Fig. 4B). There was no evidence of fibrosis in or around the capsulorrhexis or inside the capsular bag in either age group at the time of post-surgical imaging. Six months following ECLE the capsular bags (young and older) began

to exhibit the presence of pearls, fibrosis around the capsulorrhexis, and adhesions between the anterior and posterior capsular bag surfaces.

Lens capsule/CP movement

Following ECLE, CP accommodative velocity increased significantly ($p=0.02$), while movement amplitude, and the area under the CP movement curve, tended to increase ($p=0.09$), compared to the same eyes pre-surgery (Fig. 4; Table 3), regardless of age. Although the sample size is relatively small, an increased velocity post- vs. pre-ECLE with a p value of 0.02 seems meaningful. It is possible that the movement amplitude and area under the movement curve, with p values of 0.09, might also become significant with larger samples sizes (Table 3).

The pattern of increased movement occurred in both the young and older eyes (Fig. 4; Table 2), but there were age-related differences:

Young Eyes—In the young eyes during accommodation after ECLE, the lens capsule and ciliary processes tended to move faster ($p=0.082$ and 0.052 , respectively) (Fig. 4D; Table 2) and almost in a 1:1 relationship (slope of the regression line between the capsule vs. CP movement data; Fig. 5B), compared to pre-surgical baseline measurements (Fig. 4C, Fig 5A). During disaccommodation, the lens capsule and ciliary processes did not move in a 1:1 relationship in either the normal or surgically altered eyes (Figs. 5A, 5B), but the capsule vs. CP movement slope in the surgically altered eyes was significantly higher than in the normal eyes ($p<0.002$; Figs. 5A, 5B).

Older Eyes—In the 2 older rhesus eyes, the capsule velocity tended to increase post-ECLE ($p=0.088$, Table 2) but the CP velocity increase was not significant ($p=0.32$). During accommodation after ECLE, the ciliary processes and capsule moved faster (Table 2, Fig. 4F) compared to pre-surgical baseline measurements (Fig. 4E, Fig 5C), but not in a direct 1:1 relationship (Fig. 5D). Following ECLE, the area under both the CP and capsule movement curves tended to be greater ($p=0.09$, $p=0.096$ respectively), and the amplitude of capsule movement tended to be greater (by 0.16 ± 0.021 mm; $p=0.086$), than baseline before ECLE. Following ECLE, the amplitude of CP movement achieved near the end of the stimulus train was greater than baseline before ECLE (by 0.09 ± 0.019 mm; $p=0.13$) but the difference was not significant.

The increase in CP and capsule movement amplitude following ECLE was more pronounced in the older eyes (Figs. 4E, 4F) versus the young eyes (Figs. 4C, 4D). Further, in the older eyes during accommodation, the slope of the capsule vs. CP movement data steepened (Figs. 5C, 5D) after ECLE, compared to pre-surgical baseline measurements, and did so more dramatically than that in the young eyes.

Lens capsule/CP movement analysis (young vs. older)

The average movement of the lens/capsule equator in the young eyes was 0.34 mm pre-ECLE and 0.43 mm post-ECLE (Figs. 4C, 4D), and in the older eyes was 0.10 mm pre-ECLE and 0.26 mm post-ECLE (Figs. 4E, 4F). Thus, the presence of the lens substance retarded capsule movement by ~21% in the young eyes and by ~62% in the older eyes. Post-ECLE, the ratio of capsule to CP movement was 0.89 in the young eyes and 0.65 in the older eyes. Taking the ratio of these ratios and calculating the following formula: $((0.65/0.89)-1)*100 = 27\%$ gives the percent decline in capsular movement in the older eyes compared to the young eyes.

Circumlental space vs. age

In both the young and older eyes, the circumlental space (ciliary processes to capsule edge) at rest (unaccommodated) diminished following ECLE in both the nasal and temporal quadrants

(Table 4). However, during accommodation at supramaximal versus maximal settings, differences in the circumlental space were observed between the young and older eyes. In the young eyes, the circumlental space at the supramaximal stimulus setting did not diminish any further from the decrease observed at the maximal stimulus setting, pre- or post-ECLE. In the older eyes, however, the circumlental space at the supramaximal stimulus setting did diminish further compared to that at the maximal stimulus setting, both pre- and post-ECLE. At the supramaximal stimulus setting post-ECLE in the 2 older eyes, the calculated average circumlental space value was actually negative because the tips of the ciliary processes overlapped the capsule edge in 1 monkey eye, and in the eye of the other monkey the circumlental space was barely positive because the ciliary processes were so close to the capsule.

Anterior Zonule Regional Zonulolysis—Administration of α -chymotrypsin in heavy sucrose medium achieved a localized complete lysis of the anterior zonule (lysis of all zonular fibers in 2–3 clock hours between the ciliary processes and the lens edge) (Fig. 6C) in 1 quadrant (either nasal or temporal) of all 4 rhesus monkey eyes (ages 12, 23, 22, 25 yr) undergoing this procedure. The results were similar in all 4 monkeys, so the data were grouped, and average lens and CP accommodative movements calculated (Figs. 6E, 6F). Following anterior regional zonulolysis in the unaccommodated eyes, the lens equator became flattened in the lysed region (Fig. 6C), and the lens was pulled toward the opposite non-lysed region, where there was greater zonular tension (Fig 6D). During accommodation after anterior regional zonulolysis, the lens equator moved toward the sclera in the region in which zonular fibers were lysed (Fig 6E), consequent to accommodative zonular relaxation in the opposite (non-lysed) quadrant (see Video Clip #4). The lens accommodative movement in the non-lysed quadrant exceeded the pre-anterior regional zonulolysis lens edge movement in the same quadrant (Fig 6F), probably due to the shift in resting lens position toward the non-lysed quadrant. During accommodation, the lens edge convexity returned in the lysed quadrant, due to the overall release in zonular tension and decrease in lens diameter (See Video Clip #4).

Histology

Histologic examination showed that the morphology of the muscle fibers and the ciliary processes were not affected by the surgical procedures. This was true for all four quadrants of the eyes. In eyes with ICLE, the anterior zonule was present next to the pars plicata region of the ciliary processes, and the zonule appeared clumped (Fig 7.). In eyes that received ICLE +WD, no morphological changes were seen in the ciliary body, including the transition zone between pars plicata and pars plana adjacent to Wieger's ligament.

DISCUSSION

In summary: 1) Centripetal accommodative CP and capsule movement increased in velocity and amplitude post-ECLE in all 5 monkeys undergoing this procedure. 2) Centripetal accommodative CP movement was dampened in all 7 monkeys undergoing ICLE when the anterior vitreous (i.e., Wieger's ligament) was disturbed. 3) Centripetal accommodative CP movement was increased post-ICLE in 2 young monkey eyes when Wieger's ligament remained intact. 4) Anterior regional zonulolysis consistently induced a shift in lens position toward the lysed quadrant during accommodation in all 4 monkey eyes. Although these accommodative post-surgical responses occurred consistently in each monkey eye, caution is warranted in generalizing the results, given the small sample sizes of some of the groups.

Wieger's ligament (a structural part of the vitreous) may play a role in the centripetal movement of the ciliary processes and in accommodation. Following ICLE, in which Wieger's ligament was disturbed in the young eyes, the reduced velocity and the reduced amplitude of the CP

movement was most likely due to the loss of the zonula, of Wieger's ligament, and of the elastic capsule pulling the ciliary processes centripetally. Following ICLE in which Wieger's ligament remained intact, the increased CP movement was possibly due to removal of the lens substance and to the presence of intact zonular attachments between the ciliary processes and Wieger's ligament, pulling the ciliary processes centripetally. Video Clip #2 actually shows that Wieger's ligament moves centripetally during accommodation. To our knowledge, this is the first time that Wieger's ligament has been observed *in vivo* during the accommodative response (first shown in an ARVO 2004 presentation (Croft MA, et al. IOVS 2004;45:ARVO E-Abstract 2187). Bernal et al, using environmental scanning electron microscopy in later research³⁰ in human eyes, showed zonular attachments to the hyaloid membrane (Wieger's ligament). The current study demonstrates and quantifies the importance of the zonular attachment to Wieger's ligament, and confirms the importance of keeping the hyaloid and anterior zonular apparatus undisturbed for the potential restoration of (some) accommodation in presbyopes (and hopefully cataract patients), a concern that Jackson Coleman alluded to in his theory.³¹

For the two groups (ECLE and ICLE with Wieger's ligament intact), the CP accommodative and disaccommodative velocities were similar at baseline before surgery. In addition, for both groups there was an increased amplitude of accommodative CP movement compared to pre-surgical baseline (phakic eyes) (Figs. 2, Fig 4), but the velocity of disaccommodative CP movement tended to be slower (by ~40%; $p=0.066$) in the ECLE eyes versus the ICLE eyes with Wieger's ligament intact (Table 2). Collectively, the data suggests that the capsule dampens disaccommodative velocity. It is thus plausible that the capsule aids centripetal CP accommodative velocity; indeed, the velocity of accommodative CP movement averaged 24% faster post-ECLE versus post-ICLE with Wieger's ligament intact, but the difference was not statistically significant ($p=0.458$) (Table 2).

The enhanced accommodative centripetal CP and capsule dynamics in the young ECLE eyes relative to the normal eyes were most likely due to centripetal capsular elasticity being unopposed by resistance from the lens substance. The edge of the empty capsular bag moved at a faster rate during accommodation than the equator of the intact crystalline lens (Table 2, Table 3), suggesting that the lens substance, even in young accommodating monkeys, resisted capsular force. This observation is based on the following: 1) In the young eyes, the relationship between CP and capsule movement during accommodation and disaccommodation improved slightly after ECLE (slope Fig. 5); and 2) Removal of the lens substance from the older eyes significantly improved ($p<0.002$), but did not fully restore, accommodative capsule movement relative to that seen in the young monkeys. This suggests that the lens was stiffer in the older monkeys and that, after the lens was removed, age-related loss of capsular elasticity, and/or stiffening of the posterior attachment of the ciliary muscle or the posterior zonule, still prevented the ciliary processes in the older monkey eyes from moving as much as in the young monkey eyes.

The amount of centripetal accommodative capsule and CP movement post-ECLE suggests that the capsule and ciliary muscle still functioned in the older eyes. Although the older capsule-to-CP-movement ratio was reduced compared to the young eyes, the older capsules still exhibited an amount of movement (0.26 mm, Fig. 4F) that would be sufficient to induce up to 10 diopters of accommodation if an accommodating intraocular lens (IOL) with the same properties as the young crystalline lens had been in place, assuming no loss in older capsular movement. Moreover, if one were to place an accommodating IOL with the same accommodative properties as the young crystalline lens within the empty capsular bag of an older eye, it is possible to predict the amount of accommodation that may be induced. Adjusting for resistance due to the presence of the lens substance, such as in the young eyes (~21%), and adjusting for loss in capsule function observed in the older eyes versus the young eyes (~27%), the predicted amount of lens/capsule movement would be 0.15 mm in the older eyes, which

should yield 6 diopters of accommodation. (Croft MA, et al. IOVS 2005;46:ARVO E-Abstract 713) Whether the capsule in an older eye would be able to mold an accommodating IOL depends upon the characteristics of the IOL and upon how much force the capsule can still exert. Of course, caution is warranted in generalizing the results, given the small sample size of some of these groups.

In the normal monkey eyes, the circumlental space diminished at the supramaximal stimulus setting in the older eyes but not in the young eyes, due to diminished lens movement during accommodation, in line with previously published results.²³ At rest, the circumlental space tended to decrease after ECLE to a greater extent in the older eyes compared to the young eyes, suggesting an enlarged lens and/or stretched, less-elastic capsule in the older monkeys.

Folds in the capsular bag (Fig. 4) were always present following ECLE in the older monkeys, but never in the young monkeys (see Video Clip #3), suggesting that the older empty capsular bag had a larger surface area and, when emptied of the lens, was more flaccid than in young monkeys. It has been reported by others that the anterior zonulae do not change in length with age.⁸ Therefore, the “old versus young” difference might be due to growth of the lens and stretching of the capsule with age, and to increased distance between zonular insertion onto the lens and the original lens equator.⁸

Following ICLE with Wieger’s ligament disrupted, accommodative CP velocity and amplitude were reduced, but both were increased following ECLE. This suggests that, during accommodation, the lens capsule performs a dual role of: 1) reshaping the lens substance, and 2) helping to pull the ciliary processes axially and increasing the CP velocity during accommodation until zonular relaxation is achieved. The lens capsule and anterior zonule in essence form a continuous elastic sheet, acting centripetally.

Dynamic imaging of the ciliary body, lens, and zonula of the normal rhesus monkey eye with Swan-Jacob gonioscopy has provided the ability to quantitatively and qualitatively assess the normal interrelationships of the accommodative components and the normal function of the accommodative apparatus as a whole.^{20, 22, 23, 32, 33} Vilupuru et al. found that accommodative velocity was dependent upon the amplitude of accommodation in living young rhesus monkey eyes,²⁶ thus the diminished lens response amplitude in the older eyes of the current study may have resulted in diminished lens velocity. In contrast, the amplitude of the CP movement during the same period was similar in the young and older eyes, and as a result the CP velocity was not diminished in the older eyes compared to the younger eyes. Surgically altering the normal relationship between the lens and ciliary body has provided new insight into the relative roles of the lens, capsule, and ciliary body in accommodation.

Despite the complex nature of the surgical procedures and the varied amounts of time between pre- and post-surgical measurements, the results reported here and elsewhere [IOVS #0002] are consistent. Comparison of these data to previous studies in the normal (iridectomized) eye^{20, 23} lends further credence to our findings. Histologic examination showed that the three-dimensional structure of the ciliary muscle and the morphology of the muscle fibers were not affected by the surgical procedures. This, and the observed increases in accommodative movement following ECLE and ICLE with Wieger’s ligament intact, alleviate concern that these surgical procedures caused intraocular scarring that would likely diminish accommodative movements.

Following anterior regional zonulolysis, the lens position moved toward the lysed region during accommodation. This showed that the position of the lens within the eye was dependent upon zonular tension circumferentially. This also suggests that the apparent age-related shift in lens position toward the temporal quadrant, observed in the older resting eyes,²³ may be due to changes in the zonular tension with age.

Goniovideographically measured CP movement predominantly represents centripetal ciliary body movements, but goniovideography does not really distinguish centripetal from forward ciliary body movement. Thus, CP movements that we report here may actually be a hybrid or composite, in contrast to movements measured by UBM, which can isolate measurement of forward ciliary body movement. Nonetheless, the techniques of measuring forward ciliary body movement by UBM, and of centripetal CP movement by goniovideography, clearly provide separate and distinct information about ciliary body function and its change with age.²⁰

Characterization of the performance of the accommodative apparatus before and after surgical interventions may help to model the system for hypothesis testing. Information gleaned from such studies aids in understanding the accommodative mechanism itself and may also facilitate the design of accommodating intraocular lenses. Accommodating IOLs may be more effective in restoring accommodation in the presbyopic eye if they rely on centripetal ciliary body and thereby capsular edge movement rather than forward ciliary body movement.²⁰ Previous studies of accommodation in the normal iridectomized rhesus monkey eye have shown a significant age-related loss of forward ciliary body movement and lens centripetal movement, but the age-related loss in CP movement was far less pronounced.^{20, 23} Accommodative centripetal movements of the ciliary body are also still present in the presbyopic human eye,³⁴ despite the reduced accommodative amplitudes. Forward muscle movement, as measured by muscle length, was still present in excised, pharmacologically stimulated postmortem human eyes.³⁵ Whether the remaining movement is sufficient to produce accommodation with an accommodating IOL will depend on the approach and the characteristics of the accommodating IOL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Photo slitlamp images obtained through a gonioscopy lens, taken after intracapsular lens extraction (ICLE), showing intact Wieger's ligament and zonular attachments between Wieger's ligament and the ciliary processes (CP) in both the nasal (A) and temporal (B) quadrants of a 13-yr-old rhesus monkey.

Figure 2. ICLE+WI (Intracapsular Lens Extraction + Intact Wieger's ligament.) Mean $\pm$ s.e.m. of gonioscopically measured centripetal ciliary process (CP) movement (mm) in response to a 2.2-second electrical stimulus of the Edinger-Westphal (EW) nucleus pre- and post-ICLE, in which Wieger's ligament was left intact (ICLE+WI). The data are the average of 4 quadrants of 2 young monkeys (ages 6, 11 yr)

Figure 3.

(A, B) Goniovideography images before (phakic state) and after intracapsular lens extraction (ICLE) in a 6-year-old monkey eye. (C, D) Mean $\pm$ s.e.m. of gonioscopically measured centripetal ciliary process (CP) movement (mm) in response to a 2.2-second electrical stimulus of the Edinger-Westphal nucleus pre- and post-ICLE, in which Wieger's ligament was disrupted (ICLE+WD). A core vitrectomy was performed, which aspirated or disrupted ~75% of the anterior vitreous. Top panel (C) shows the average of 6 quadrants of 3 young monkeys (ages 6, 8, 9 yr). Bottom panel (D) shows the average of 7 quadrants of 4 older monkeys (ages 18, 19, 19, 27 yr).

Figure 4.

(A) Goniovideography image post-extracapsular lens extraction (ECLE) in a young (age 6 yr) monkey eye, 11 weeks post-surgery. (B) Goniovideography image post-ECLE in an older (age 23 yr) monkey eye, 5 weeks post-surgery. Both the young and older capsules appeared semi-transparent with no evidence of pearls or anterior-posterior capsule adhesions or fibrosis and no obvious scarring. (C, D, E, F) Data are the mean $\pm$ s.e.m. of gonioscopically measured centripetal CP and lens or capsule movement pre- and post-ECLE in 5 quadrants of 3 young (ages 6, 7, 9 yr) and 4 quadrants of 2 older (ages 21, 23 yr) monkey eyes.

Figure 5.

Gonioscopically measured ciliary process (CP) movement versus lens or capsule movement, plotted using the data in Figure 4. The numbers in the panels represent the simple linear regression slope of lens or capsule versus CP movement $\pm$ s.e.m. during accommodation and disaccommodation. All regression slopes tended to be less than 1.0 ($p < 0.04$). * The slope post-ECLE tended to be higher compared to pre-ECLE ($p < 0.002$).

Figure 6.

Ciliary process (CP) and lens movement pre- (A, B) and post- (C, D) anterior regional zonulolysis (ARZ) in 1 quadrant of 1 rhesus monkey eye (age 23 yr). (E, F) Data are mean $\pm$ s.e.m. of gonioscopically measured CP and lens movement in both quadrants (nasal and temporal) of 4 rhesus monkey eyes (ages 13, 23, 23, 25 yr) pre- and post-ARZ in 1 quadrant.

Figure 7.

Semithin (1 μ m) sagittal section through the anterior inner portion of the ciliary muscle and the adjacent ciliary processes and zonule in rhesus monkey eye following (A) extracapsular lens extraction (ECLE) and (B) intracapsular lens extraction (ICLE). Note that the muscle fibers and entire ciliary epithelium are intact. In eyes with ICLE the zonule is still present in the attachment zones at the inner limiting membrane of the epithelium and the adjacent anterior and posterior chamber.

Table 1

Division of study animal eyes according to age and surgical procedure

	ICLE	ECLE	ARZ
Young (n=9) (6–13 yr)	5 [*]	3	1
Older (n=9) (17–27 yr)	4 ^{**}	2	3
Total (n=18)	9	5	4

(ICLE = intracapsular lens extraction. ECLE = extracapsular lens extraction. ARZ = anterior regional zonulolysis.)

^{*} This group was further divided according to whether Wieger's ligament was intact (n=2) or disturbed (n=3).^{**} This group was comprised of ICLE eyes in which Wieger's ligament was disrupted (see page 10, section entitled "Intracapsular lens extraction (ICLE)").

Table 2
Ciliary Process (CP) and Lens Velocity in Normal and Post Surgical Eyes

Data represent mean $\pm$ s.e.m. of gonioscopically measured ciliary process (CP) and lens velocity²² in normal and post-surgical eyes during supramaximal stimulation.

		Velocity (mm/sec)	
A. Normal Eyes		Young	Older
Accommodation	CP	0.77 $\pm$ 0.054	0.67 $\pm$ 0.072
	Lens	0.68 $\pm$ 0.047	0.34 $\pm$ 0.032 //
Disaccommodation	CP	-0.98 $\pm$ 0.15	-1.28 $\pm$ 0.18
	Lens	-0.73 $\pm$ 0.11	-0.46 $\pm$ 0.051 $\ddagger$
		Young n= 8 eyes; 15 quadrants	Older n= 15 eyes; 30 quadrants
B. Surgically Treated Eyes		ICLE-WD (Wieger's Ligament Disrupted)	
		Young	Older
Accommodation	CP	Baseline 0.69 $\pm$ 0.082	Baseline 0.32 $\pm$ 0.049
	CP	Post Surgery 0.41 $\pm$ 0.087 //	Post Surgery 0.22 $\pm$ 0.045
Disaccommodation	CP	Baseline -1.16 $\pm$ 0.297	Baseline -0.67 $\pm$ 0.163
	CP	Post Surgery -0.87 $\pm$ 0.190	Post Surgery -0.34 $\pm$ 0.075 *
		Young n= 3 eyes; 6 quadrants	Older n= 4 eyes; 7 quadrants
		ICLE-WI (Wieger's Ligament Intact)	
		Young	
Accommodation	CP	Baseline 0.70 $\pm$ 0.120	Post Surgery 0.72 $\pm$ 0.060
	CP	Post Surgery -1.11 $\pm$ 0.201	Post Surgery -1.47 $\pm$ 0.284
		Young n= 2 eyes; 4 quadrants	
ECLE		Young	Older
Accommodation	CP	Baseline 0.75 $\pm$ 0.180	Baseline 0.54 $\pm$ 0.119
	Lens/Capsule	0.69 $\pm$ 0.137	0.24 $\pm$ 0.008
Disaccommodation	CP	Post Surgery -0.85 $\pm$ 0.046	Post Surgery -0.68 $\pm$ 0.377
	Lens/Capsule	-0.75 $\pm$ 0.039	-0.26 $\pm$ 0.071
		Young n= 3 eyes; 5 quadrants	Older n= 2 eyes; 4 quadrants

Comparisons between young versus older eyes (A) or between pre- and post-surgical measurements (B) by the two-tailed paired t-test:

* p<0.054;

[†] p=0.088
[‡] p=0.082
[§] p=0.052
^{||} p=0.034.

The s.e.m. reported in this table are pooled values from two quadrants for each eye (nasal and temporal) with two exceptions: one older ICLE+WD eye provided data from one quadrant and one young ECLE eye provided data from one quadrant.

Table 3
CP and Lens/Capsule Movement Data in Young and Older eyes Combined Pre (Baseline) and Post Surgery

Data represent mean $\pm$ s.e.m. of gonioscopically measured ciliary process (CP) and lens/capsule movement velocity, amplitude, and area under the movement curve (averaged from both nasal and temporal quadrants) in normal and post-surgical eyes during supramaximal stimulation, grouped regardless of age.

CP movement	ICLE+Wieger's Ligament Disturbed		Difference	p-value n=7
	Baseline	Post ICLE+WD		
Amplitude (mm)	0.35 $\pm$ 0.056	0.26 $\pm$ 0.053	-0.09 $\pm$ 0.042	0.072
Area under curve (mm-sec)	0.72 $\pm$ 0.118	0.52 $\pm$ 0.107	-0.19 $\pm$ 0.084	0.060
Accommodation Velocity (mm/sec)	0.48 $\pm$ 0.086	0.31 $\pm$ 0.056	-0.17 $\pm$ 0.062	0.03
Disaccommodation Velocity (mm/sec)	-0.88 $\pm$ 0.173	-0.57 $\pm$ 0.135	0.31 $\pm$ 0.109	0.03
n=7 [Young eyes (n=3; ages 6, 8, 9 yr); Older eyes (n= 4; ages 18, 19, 19, 27 yr)]				
CP movement	ICLE+Wieger's Ligament Intact		Difference	p-value n=2
	Baseline	Post ICLE+WI		
Amplitude (mm)	0.44 $\pm$ 0.05	0.55 $\pm$ 0.05	0.11 $\pm$ 0.038	0.22
Area under curve (mm-sec)	0.91 $\pm$ 0.097	1.09 $\pm$ 0.155	0.18 $\pm$ 0.058	0.20
Accommodation Velocity (mm/sec)	0.70 $\pm$ 0.120	0.72 $\pm$ 0.060	0.02 $\pm$ 0.05	NS
Disaccommodation Velocity (mm/sec)	-1.11 $\pm$ 0.201	-1.47 $\pm$ 0.284	-0.37 $\pm$ 0.25	NS
Young eyes (n=2; ages 8, 11.5 yr)				
CP movement	ECLE		Difference	p-value n=5
	Baseline	Post ECLE		
Amplitude (mm)	0.39 $\pm$ 0.054	0.47 $\pm$ 0.075	0.08 $\pm$ 0.036	0.094
Area under curve (mm-sec)	0.81 $\pm$ 0.124	0.98 $\pm$ 0.178	0.17 $\pm$ 0.079	0.092
Accommodation Velocity (mm/sec)	0.67 $\pm$ 0.118	0.84 $\pm$ 0.158	0.17 $\pm$ 0.043	0.016
Disaccommodation Velocity (mm/sec)	-0.85 $\pm$ 0.146	-0.90 $\pm$ 0.069	-0.05 $\pm$ 0.131	NS
n=5 [Young eyes (n=3; ages 6, 7, 9 yr); Older eyes (n= 2; ages 22, 23 yr)]				
Lens/Capsule movement	ECLE		Difference	p-value n=5
	Baseline	Post ECLE		
Amplitude (mm)	0.26 $\pm$ 0.071	0.38 $\pm$ 0.072	0.12 $\pm$ 0.027	0.012
Area under curve (mm-sec)	0.56 $\pm$ 0.153	0.80 $\pm$ 0.163	0.24 $\pm$ 0.067	0.022
Accommodation Velocity (mm/sec)	0.51 $\pm$ 0.135	0.72 $\pm$ 0.134	0.21 $\pm$ 0.032	0.002
Disaccommodation Velocity (mm/sec)	-0.54 $\pm$ 0.127	-0.73 $\pm$ 0.028	-0.20 $\pm$ 0.111	0.152
n=5 [Young eyes (n=3; ages 6, 7, 9 yr); Older eyes (n= 2; ages 22, 23 yr)]				

The p-value was obtained from a two-tailed paired t-test. The paired observation was between the pre-surgical response (Baseline) vs post surgical response within each eye. The s.e.m. reported in this table are pooled values from two quadrants for each eye (nasal and temporal) with two exceptions: one older ICLE+WD eye provided data from one quadrant and one young ECLE eye provided data from one quadrant. provided data from one quadrant.

Circumlental Space at Rest and During Stimulation Before and After Extracapsular Lens Extraction Circumlental Space (mm)

Data are mean $\pm$ s.e.m. of gonioscopically measured circumlental space in the resting, maximal (Max), and supramaximal (Smax) stimulated states before and after extracapsular lens extraction (ECLE). In the 2 older eyes at the Smax stimulus setting post-ECLE, the calculated average circumlental space value was actually negative because the tips of the ciliary processes overlapped the capsule edge in 1 monkey.

		Post ECLE									
		Baseline (Phakic eye)									
		Unaccommodated Nasal	Unaccommodated Temporal	Max Nasal	Max Temporal	Smax Nasal	Smax Temporal	Unaccommodated Nasal	Unaccommodated Temporal	Max Nasal	Max Temporal
Young (n=3)	Mean	0.54	0.45	0.43	0.38	0.41	0.36	0.32	0.27	0.23	0.25
	s.e.m.	0.040	0.056	0.039	0.077	0.049	0.068	0.051	0.002	0.045	0.060
Older (n=2)	Mean	0.46	0.35	0.38	0.21	0.25	0.14	0.17	0.10	0.05	0.00
	s.e.m.	0.08	0.05	0.02	0.10	0.04	0.07	0.02	0.11	0.06	0.19
Circumlental Space Baseline Minus Post ECLE differences (mm)											
		Unaccommodated Nasal		Max Nasal		Smax Nasal		Unaccommodated Temporal		Max Temporal	
Young Older		0.23	0.29	0.18	0.25	0.20	0.33	0.14	0.21	0.19	0.27