Comparisons between Pharmacologically and Edinger-Westphal–Stimulated Accommodation in Rhesus Monkeys

Lisa A. Ostrin and Adrian Glasser

Purpose. Accommodation results in increased lens thickness and lens surface curvatures. Previous studies suggest that lens biometric accommodative changes are different with pharmacological and voluntary accommodation. In this study, refractive and biometric changes during Edinger-Westphal (EW) and pharmacologically stimulated accommodation in rhesus monkeys were compared.

Methods. Accommodation was stimulated by an indwelling permanent electrode in the EW nucleus of the midbrain in one eye each of four rhesus monkeys. Dynamic refractive changes were measured with infrared photorefraction, and lens biometric changes were measured with high-resolution, continuous A-scan ultrasonography for increasing stimulus current amplitudes, including supramaximal current amplitudes. Accommodation was then stimulated pharmacologically and biometry was measured continuously for 30 minutes.

Results. During EW-stimulated accommodation, lens surfaces move linearly with refraction, with an increase in lens thickness of 0.06 mm/D, an anterior movement of the anterior lens surface of 0.04 mm/D, and a posterior movement of the posterior lens surface of 0.02 mm/D. Peak velocity of accommodation (diopters per second) and lens thickness (in millimeters per second) increased with supramaximal stimulus currents, but without further increase in amplitude or total lens thickness. After carbachol stimulation, there was initially an anterior movement of the anterior lens surface and a posterior movement of the posterior lens surface; but by 30 minutes, there was an overall anterior shift of the lens.

Conclusions. Ocular biometric changes differ with EW and pharmacological stimulation of accommodation. Pharmacological stimulation results in a greater increase in lens thickness, an overall forward movement of the lens and a greater change in dioptric power. (*Invest Ophthalmol Vis Sci.* 2005;46: 609–617) DOI:10.1167/iovs.04-0990

Accommodation is a dioptric increase in power of the eye due to contraction of the ciliary muscle, allowing the crystalline lens to assume a more accommodated form.[1] When this occurs, lens diameter decreases,[2–4] central curvature of the anterior and posterior lens surfaces increases,[5–7] and axial thickness of the lens increases.[8,9] This results in an anterior movement of the anterior lens surface and a posterior movement of the posterior lens surface.[10–12] Previous studies in rhesus monkeys, in which A-scan ultrasound biometry was used, have shown that lens thickness increases an average of 0.063 mm/D of accommodation, with approximately 75% of the increase due to anterior movement of the anterior lens surface and the remainder due to posterior movement of the posterior lens surface.[12,13]

Pharmacological stimulation has frequently been used to induce and study accommodation in both humans[14–18] and nonhuman primates.[2,8,19,20] Recently, investigators studying accommodative restorative procedures, such as potentially accommodative IOLs and scleral expansion, have used pharmacological stimulation to test IOL movement[21] and whether accommodative amplitude increases after surgery.[14,22–24] Pharmacological stimulation results in an involuntary accommodative response without producing convergence eye movements that are usually coupled with voluntary accommodation. Pharmacological stimulation can be used to elicit accommodation in presbyopes who have little voluntary accommodation.[15]

Pharmacological stimulation using 2% pilocarpine induces accommodative changes in young subjects[25] and phakic presbyopes (Findl O, et al. *IOVS* 2004;45:E-Abstract 1744) that are different from what is elicited voluntarily. Pilocarpine stimulation caused a similar change in lens thickness as voluntary accommodation, but with an anterior shift in the posterior lens surface. Another study measured an anterior shift in the posterior lens surface in 33% of subjects with ultrasound biometry after 2% pilocarpine stimulation.[26] Therefore, pharmacologically stimulated accommodation may produce accommodative responses that are different from those achieved with voluntary accommodation. This is important to know, especially if pharmacologically stimulated accommodation is used to assess accommodative restoration procedures or accommodative IOLs that are designed to shift forward with an accommodative effort.[21,27,28]

In humans, visual stimulus-driven accommodation is an accommodative response to blur or a proximal stimulus. When the target is perceived, a neuronal response passes from the brain to the ciliary muscle via the parasympathetic pathway. Endogenous neurotransmitter, acetylcholine, is released at the intraocular neuromuscular junctions to cause a ciliary muscle contraction and pupil constriction and at extraocular neuromuscular junctions to cause convergence. If an accommodative response is to occur, the subject must produce an accommodative effort. Pharmacological stimulation, however, allows a muscarinic agonist delivered to the eye to reach the cholinergic receptors on the ciliary muscle through diffusion and to bind directly to those receptors to produce a ciliary muscle contraction. This requires no voluntary effort to accommodate and does not rely on the neuronally controlled accommodative response. In rhesus monkeys, another approach used to induce accommodation is through stimulation of the Edinger-Westphal (EW) nucleus.[2,29,30] As with visual stimulus-driven accommodation, the neuronal impulses from the brain to the ciliary muscle cause the ciliary muscle contraction. Whereas the

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Corresponding author: Adrian Glasser, Houston College of Optometry, 505 J. Armistead Building, Houston, TX 77204; aglasser@uh.edu.

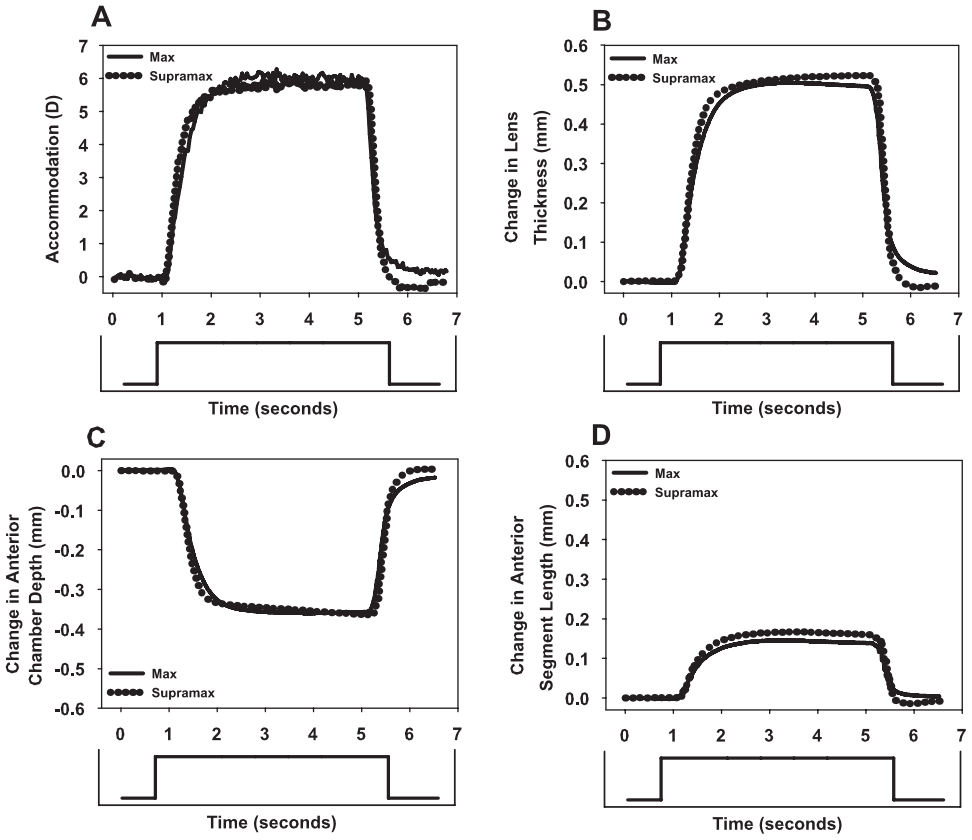

FIGURE 1. Refractive (**A**) and biometric (**B–D**) changes during EW stimulation are shown for monkey 4 for maximal and supramaximal stimulus current amplitudes. (**D**) Anterior segment length is represented by anterior chamber depth + lens thickness.

source of the EW-stimulated response is an artificial stimulation delivered to the midbrain, contraction of the ciliary muscle is still achieved through endogenous neurotransmitter release at the ciliary neuromuscular junctions.

The goal of this study was to compare anterior segment ocular biometric changes during EW-stimulated and pharmacologically stimulated accommodation in adolescent rhesus monkeys.

METHODS

Accommodation experiments were performed in one eye each of four rhesus monkeys (*Macaca mulatta*), ages 12 (monkey 4), 4 (monkey 111), and 5 (monkeys 38 and 70) years. The monkeys had previously undergone bilateral, complete iridectomies[31] and had had stimulating electrodes surgically implanted in the EW nucleus of the midbrain.[29] The monkeys are used in multiple experimental protocols,[12,32] and the iridectomies,[31] justification for them,[33] and absence of an effect on EW-stimulated accommodation[34] have been described previously. All experiments conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were conducted under an institutionally approved animal protocol.

Animal Preparation

Monkeys were initially anesthetized with 10 mg/kg intramuscular ketamine and 0.5 mg/kg intramuscular acepromazine. Surgical depth anesthesia was maintained for the duration of the experiment with intravenous propofol (Propoflo; Abbott Laboratories, North Chicago, IL), with an initial bolus of 0.15 mg/kg followed by constant perfusion of 0.5 mg/kg per minute. Monkeys were placed prone with the head facing forward in a head holder, and sutures were tied beneath the lateral and medial rectus muscles of the eye, to reduce convergent eye movements during accommodation.[2] The eyelid was held open with a lid speculum, and a custom-made PMMA contact lens (MetroOptics, Austin, TX) was placed on the cornea to maintain optical quality and corneal hydration.[32]

Static EW-stimulated accommodative responses were first measured in one eye with a Hartinger coincidence refractometer[35] (Carl Zeiss Meditec, Jena, Germany) to generate an accommodative stimulus-response function. The static Hartinger stimulus-response function was later used to calibrate both the dynamic photorefraction and biometric measurements. Accommodation was stimulated using 2-second stimulus trains, from 0 μA up to a current amplitude sufficient to produce the maximal accommodative response available to that eye. In addition, three further increasing supramaximal stimulus current amplitudes were delivered to each eye. For each stimulus amplitude, the accommodative responses to three 2-second long stimulus trains were measured in succession and averaged.

Photorefraction Measurements

To study the accommodative dynamics, infrared photorefraction was used to measure dynamically the accommodative refractive change and to determine the relationship between the peak velocity and the amplitude of the accommodative responses (a main sequence relationship).[36] Photorefraction was performed at a 0.3-m working distance using a charge-coupled device (CCD) camera (Cohu, San Diego, CA) with a bank of infrared LEDs mounted on a knife-edge aperture.[2,32,37,38] Images were captured to video at 30 Hz and analyzed frame-by-frame off-line using image-analysis software (Optimas; Media Cybernetics, Silver Springs, MD). Photorefraction images were analyzed over the central 40% of the iridectomized pupil diameter to measure the slope of the vertical luminance profile. Photorefraction was calibrated to convert the measured slopes into refraction using the static stimulus response function for the same stimulus amplitudes measured with a Hartinger coincidence refractometer.[32]

Biometric Measurements

Biometric changes were measured with continuous high-resolution A-scan ultrasound biometry (CUB).[39] Biometric measurements were recorded to computer at 100 Hz, using a 10-MHz transducer. A rubber stand-off sleeve was placed over the transducer tip and filled with ultrasound transmission gel (Liquasonic Ultrasound gel; Chester Laboratories, Inc., Cincinnati, OH), and the transducer was clamped in a micromanipulator. The contact lens was removed from the eye, and the transducer was aligned along the optical axis of the eye with the manipulator. The transducer contacted the cornea through the gel to generate sharp A-scan peaks representing the anterior and posterior cornea surfaces, anterior and poster lens surfaces, and the retina. The CUB measures the time between peaks associated with the intraocular surfaces. These times are converted to distances off-line using standard, accepted sound velocities: anterior and vitreous chambers, 1532 m/s, and lens, 1641 m/s.[8,12,40]

Biometric changes were recorded during a sequence of increasing EW-stimulated accommodative responses. The same stimulus current amplitudes used during the photorefraction measurements described earlier were used for the CUB measurements.

After EW stimulation, the transducer was removed from the eye, and the eye was irrigated with saline. Accommodation was then stimulated with carbachol iontophoresis.[29,32] Carbachol (40%) in agar gel was applied iontophoretically for 8 seconds each to the nasal and temporal corneal margins.[32] The eye was immediately irrigated, and the CUB transducer with transmission gel was replaced in contact with the cornea. Biometric changes were recorded continuously with the CUB at 1 Hz for 30 minutes after carbachol instillation.

Data Analysis

Biometric data from EW-stimulated accommodation was recorded as anterior chamber depth and lens thickness. To compare the 100-Hz CUB biometric changes directly with the 30-Hz photorefraction refraction changes during EW-stimulated accommodation, the CUB data were subsequently resampled at 30 Hz. Changes in anterior lens surface position were determined from measurements of anterior chamber depth, and changes in posterior lens surface position were determined by adding anterior chamber depth and lens thickness (anterior segment length). Lens movements were statistically analyzed with paired *t*-tests, using $P < 0.05$ as the significance level.

Main sequence relationships (peak velocity as a function of amplitude) for accommodative and disaccommodative refractive and biometric responses were established. The accommodative responses were plotted as a function of time for both photorefraction and biometry, and exponential curves were fitted to the accommodation phases and the disaccommodation phases.[32] The derivative of these functions with respect to time gives the velocity profile of the responses.[32] The V_{max} achieved for each accommodative response is the peak velocity.

Results

Refractive and biometric changes from maximal and supramaximal stimulus current amplitudes are shown for monkey 4 in Figure 1. During accommodation, lens thickness increased, anterior chamber depth decreased, and anterior segment length (anterior chamber depth + lens thickness) increased, reflecting a posterior movement of the posterior lens surface. Movement of the anterior and posterior lens surfaces occurred relatively linearly with accommodation after EW stimulation (Figs. 2). There was a small net anterior movement of the center of the lens (Figs. 3; Table 1) with accommodation. The changes are not systematically different between the maximal and supramaximal stimulus levels. Biometry was measured subsequent to refraction, so nonlinearities (monkey 70) are due to slight variations in the responses to the same stimulus amplitudes.

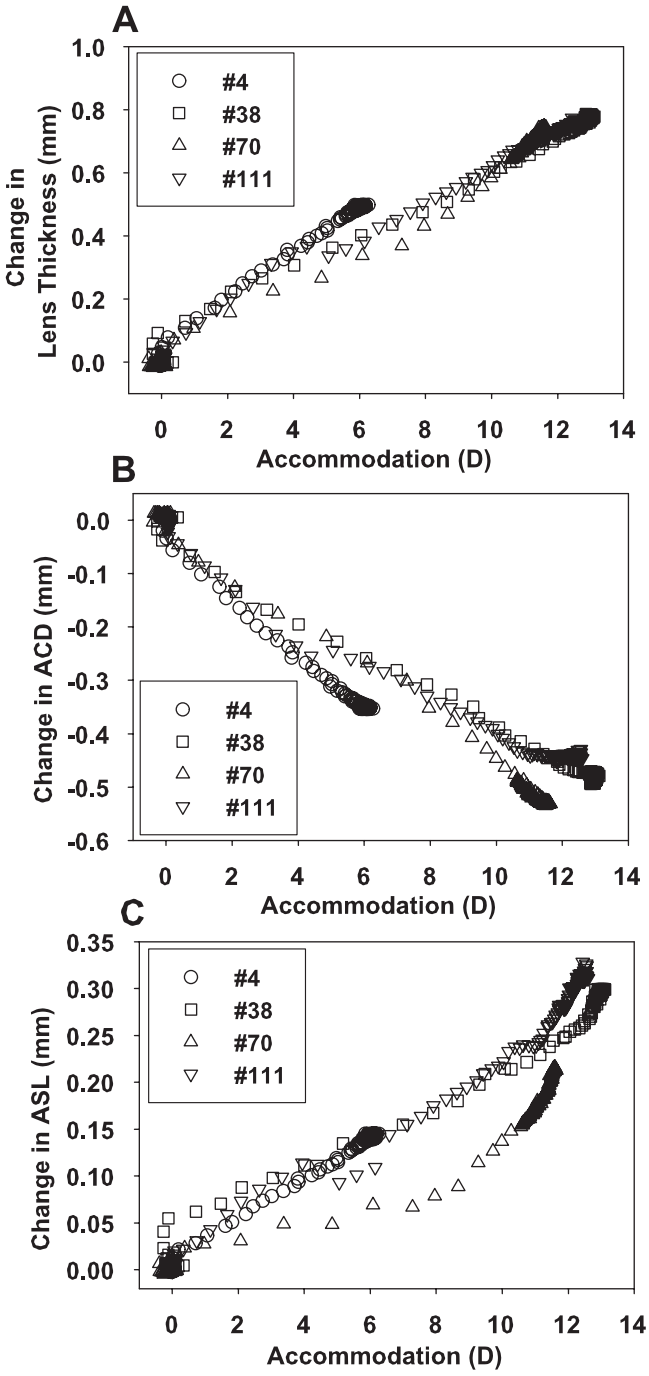

Figure 2. Accommodative refractive changes related to the biometric changes during EW stimulation for (**A**) lens thickness; (**B**) anterior chamber depth (ACD) and (**C**) anterior segment length (ASL). Data shown are from a single stimulus current amplitude that provides a maximal accommodative response for each monkey.

Within 2 to 8 minutes after carbachol iontophoresis (the "initial phase"), the anterior lens surface moved anteriorly, and the posterior lens surface moved posteriorly relative to their unaccommodated positions (Fig. 4). Subsequently, over the next 20 minutes (the "final phase"), there was a continued further forward movement of the anterior lens surface and the posterior lens surface moved anteriorly (Table 2). By 30 minutes, the posterior lens surface of two monkeys (4 and 38) had moved anterior of the starting (rest) position. The posterior lens surface of one monkey (monkey 111) was close to its

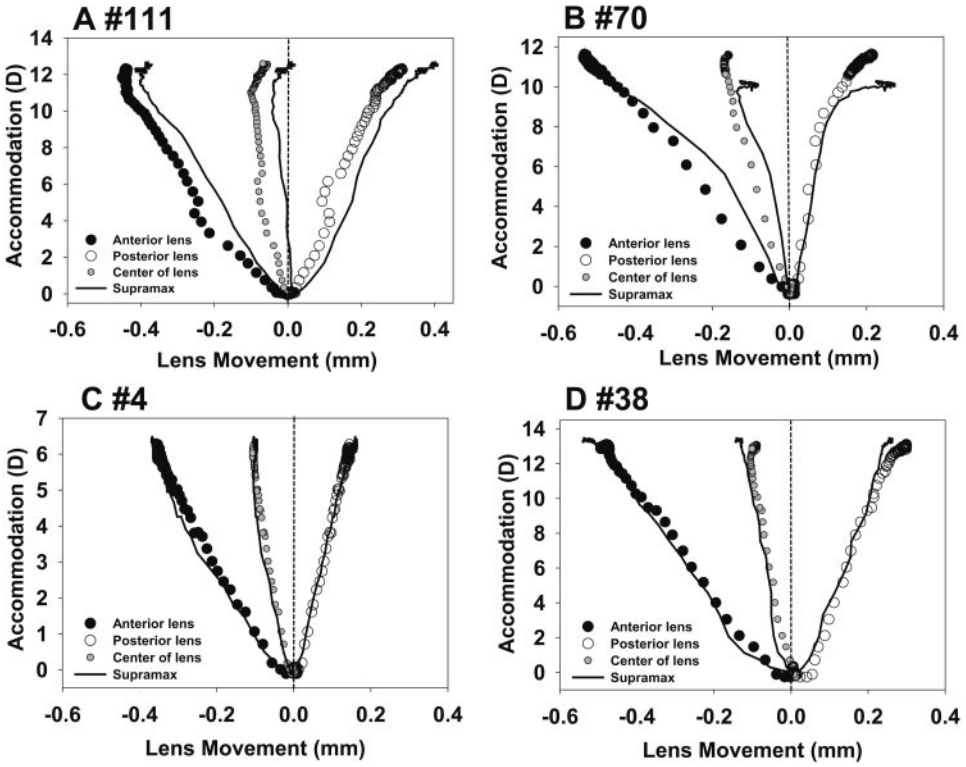

FIGURE 3. The accommodative movements of the anterior lens surface, the posterior lens surface, and the center of the lens after maximal and supramaximal EW stimulation of accommodation in monkeys (**A**) 111, (**B**) 70, (**C**) 4, and (**D**) 38.

starting position, and in one monkey (monkey 70) was posterior to its starting position.

Lens movements and accommodation (where available) were similar for maximal EW stimulation, supramaximal EW stimulation, and the initial phase of carbachol stimulation (Table 1). Lens position was significantly different between the resting state and maximal EW-stimulated accommodation (anterior lens surface, $P < 0.05$; posterior lens surface, $P < 0.05$; center of lens, $P < 0.05$). Lens position during EW-stimulated accommodation was not different for maximal and supramaximal current amplitudes (anterior lens surface, $P = 0.62$; posterior lens surface, $P = 0.43$; center of lens $P = 0.50$). Lens position was also not different for maximal EW stimulation and the carbachol initial phase (anterior lens surface, $P = 0.92$; posterior lens surface, $P = 0.51$; center of lens, $P = 0.35$). However, lens position ultimately achieved with carbachol stimulation (30 minutes after instillation) was significantly different from that achieved with maximal and supramaximal EW stimulation ($P < 0.05$ for all parameters). The position of the posterior lens surface 30 minutes after carbachol was not significantly different from its starting (rest) position ($P = 0.89$, Table 2).

The final lens thickness with maximal EW-stimulated accommodation was significantly thicker than at the resting state ($P < 0.05$). Total change in lens thickness was not different for maximal versus supramaximal current stimulation ($P = 0.58$) and maximal current versus the carbachol initial phase ($P = 0.74$). Total change in lens thickness was significantly greater 30 minutes after carbachol stimulation than for both stimulus current amplitudes ($P < 0.05$, Fig. 5; Table 1).

The change in refraction during carbachol iontophoresis could not be measured while the CUB transducer was on the eye or after 30 minutes of having gel on the cornea due to loss of corneal clarity. Therefore, the accommodative amplitude after carbachol stimulation was determined as the average of two to five carbachol experiments performed on the same eyes in the previous 6 months (Fig. 6A). The time course of the carbachol iontophoresis induced accommodative response was relatively consistent for the same eye between experiments. Carbachol-induced accommodation was significantly greater than maximal and supramaximal EW-stimulated accommodation ($P < 0.05$, Fig. 6B; Table 1). Although movements of the anterior lens surface, posterior lens surface, and center of the lens per diopter of accommodation were similar for maximal and supramaximal EW stimulation ($P = 0.66$, $P = 0.34$, and $P = 0.43$, respectively), these per diopter changes were significantly different from pharmacological stimulation measured 30 minutes after carbachol iontophoresis ($P < 0.05$, Table 3). Changes in lens thickness per diopter of accommodation were not significantly different for maximal and supra-

TABLE 1. Lens Movements with EW and Pharmacologically Stimulated Accommodation

Method	Anterior Lens Surface	Posterior Lens Surface	Center of Lens	Increase in Lens Thickness	Accommodation (D)
EW stimulation, max current	−0.45 ± 0.08	+0.24 ± 0.08	−0.11 ± 0.04	+0.69 ± 0.13	10.75 ± 3.21
EW stimulation, supramax current	−0.44 ± 0.08	+0.26 ± 0.10	−0.09 ± 0.07	+0.70 ± 0.12	10.61 ± 3.16
Carbachol stimulation initial phase	−0.48 ± 0.15	+0.19 ± 0.06	−0.14 ± 0.05	+0.67 ± 0.21	NA
Carbachol stimulation at 30 minutes	−0.82 ± 0.12	−0.017 ± 0.16	−0.42 ± 0.12	+0.80 ± 0.15	14.73 ± 3.30

For the lens, a negative value represents an anterior movement and a positive value represents a posterior movement. Data are the averages from four eyes expressed as millimeters ± SD for lens movements and D ± SD for accommodation.

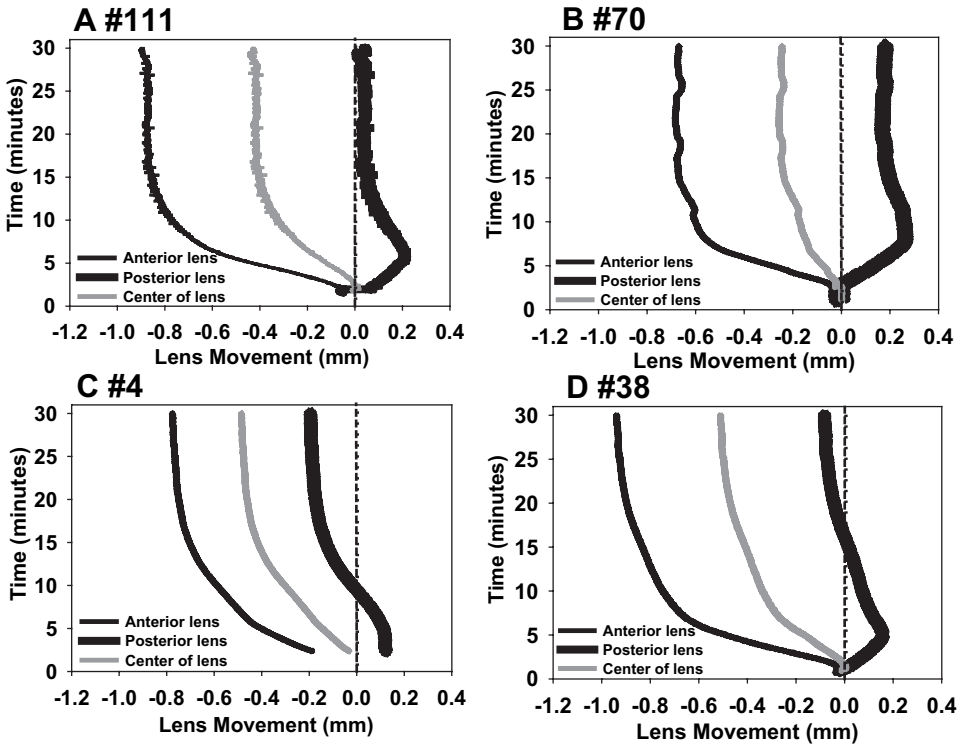

FIGURE 4. The time course of the accommodative biometric changes for the anterior lens surface, the posterior lens surface, and the center of the lens after pharmacological stimulation of accommodation with carbachol iontophoresis in the eyes of monkeys (**A**) 111, (**B**) 70, (**C**) 4, and (**D**) 38. (**C**) The initial accommodative change immediately after carbachol iontophoresis was not recorded because it took approximately 2 minutes before the CUB transducer could be correctly aligned and data collection could begin.

maximal EW stimulation ($P = 0.29$), maximal EW stimulation and pharmacological stimulation ($P = 0.16$) or supramaximal EW stimulation and pharmacological stimulation ($P = 0.11$). The increase in lens thickness for maximal EW stimulation was 0.067 mm/D, for supramaximal stimulation was 0.069 mm/D, and at 30 minutes after pharmacological stimulation was 0.055 mm/D.

Accommodative dynamics were determined in terms of peak velocity of accommodative amplitude and lens thickness (main sequence relationships) for both accommodation and disaccommodation (Fig. 7). The data were normalized to the current amplitude, which caused a maximal response in each eye. Accommodation and disaccommodation were normalized independently because, after an accommodative response, the eye sometimes returns to a slightly different unaccommodated resting state (see Fig. 1). For accommodation, the refractive and biometric main sequence relationships increased linearly for stimulus current amplitudes up to a current amplitude, which elicited the maximal accommodative response. For supramaximal current amplitudes, the peak velocity of accommodation increased without a further change in refraction or lens thickness. For disaccommodation, main sequence relationships were linear for all stimulus current amplitudes, including supramaximal stimuli. Linear regression slopes of the main sequence relationships fitted to the nonsupramaximal data were not significantly different between refraction and biometry for accommodation ($F_{(2,44)} = 1.26$, $P = 0.29$) or disaccommodation ($F_{(2,50)} = 0.48$, $P = 0.62$). Disaccommodative refractive changes were no greater for supramaximal versus maximal stimulus amplitudes, but disaccommodative lens thickness changes were slightly greater for supramaximal versus maximal stimulus amplitudes (Fig. 7C).

TABLE 2. Movements of the Posterior Lens Surface with Pharmacologically Stimulated Accommodation

Monkey	Initial Posterior Movement	Subsequent Anterior Movement	Final Position
111	+0.21	−0.17	+0.04
44	+0.12	−0.32	−0.19
70	+0.26	−0.08	+0.18
38	+0.16	−0.24	−0.082
Average	+0.19 ± 0.062	−0.20 ± 0.10	−0.017 ± 0.16

After carbachol stimulation, all monkeys showed an initial posterior movement of the posterior lens surface, followed by an anterior movement. The initial phase is considered to be up to the inflection point for the posterior movement of the posterior lens surface. A negative value represents an anterior movement and a positive value represents a posterior movement. All values are millimeters ± SD.

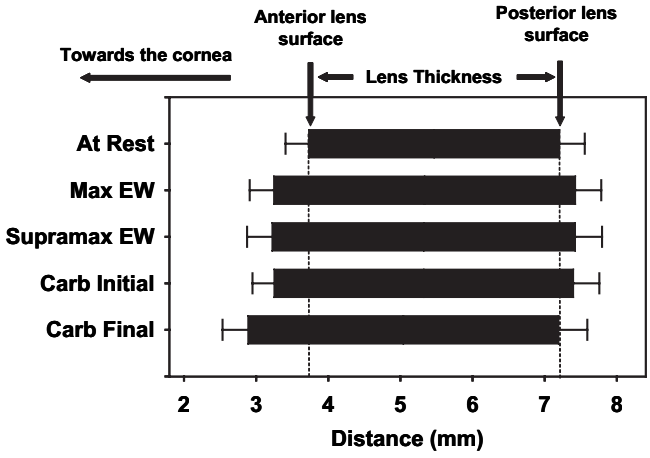

FIGURE 5. Lens thickness at rest and under various accommodative stimuli is shown. The movement of the anterior and posterior lens surfaces is shown relative to the rest position for maximal (Max EW) and supramaximal (Supramax EW) EW stimulation, the initial carbachol (Carb Initial) phase, and at 30 minutes after carbachol delivery (Carb Final). Error bars, SEM.

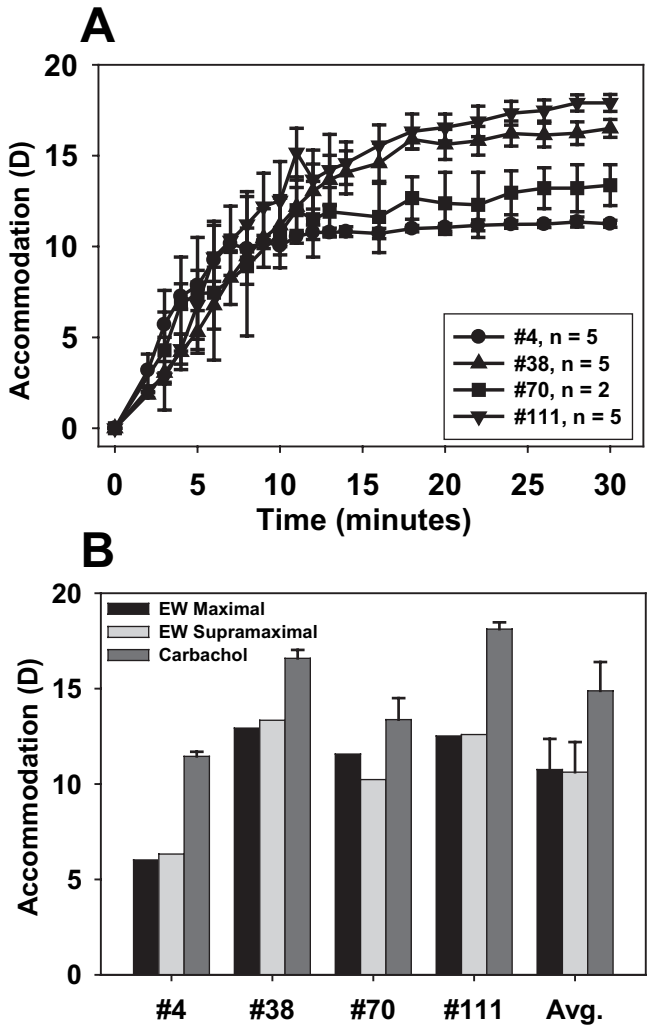

FIGURE 6. (**A**) Time course of the carbachol-stimulated accommodative response, as determined from two to five prior experiments on the same eyes in the four monkeys. (**B**) Comparison of the accommodative amplitudes for maximal and supramaximal EW stimulation and carbachol stimulation in all monkeys. Error bars, SEM.

DISCUSSION

The results of this study indicate that biometric changes during EW- and pharmacologically stimulated accommodation are different. EW-stimulated accommodation results in an anterior movement of the anterior lens surface, a posterior movement of the posterior lens surface, and an anterior movement of the center of lens. Carbachol iontophoretically stimulated accommodation also initially results in the same accommodative changes in the lens. However, this is subsequently followed by an anterior movement of the entire lens.

In this study, the monkeys were iridectomized. It is possible that the presence or absence of the iris may influence the accommodative biometric changes of the lens. A previous study in monkeys has shown that (1) maximal carbachol-stimulated accommodative amplitude is 40% less in iridectomized eyes compared with contralateral normal eyes, (2) submaximal pilocarpine stimulated accommodative amplitude is similar in normal and iridectomized eyes, and (3) maximal centrally stimulated accommodative amplitude is similar in normal and iridectomized eyes.[34] The investigators hypothesized that maximal pharmacological stimulation, which produces a strong pupil constriction, results in the ciliary body's being pulled forward to enhance the accommodative response. The similar accommodative amplitudes achieved with centrally stimulated accommodation and with submaximal pharmacologically stimulated accommodation, irrespective of the presence or absence of the iris, argue that the accommodative response, at least insofar as amplitude is concerned, is not dependent on the iris. Previous studies have shown similar biometric changes in human eyes in the presence of the iris as reported in the present study in iridectomized monkey eyes.[11,25] This suggests that whereas the presence or absence of the iris may alter the amplitude of the effects reported, it is not likely to alter the overall results.

Carbachol is a strong parasympathetic agonist and a supramaximal dose causes ciliary muscle contraction and greater accommodative response than is achieved with EW stimulation.[29] Therefore, supramaximal stimulus currents were delivered to the EW nucleus and the responses were measured with the CUB to determine whether a forward movement of the lens also occurs with supramaximal current stimulation. Although the peak velocity of both refraction and lens thickness increased with supramaximal stimulus currents for accommodation, an anterior shift of the entire lens was not observed. The increase in peak velocity without a further increase in accommodation (as assessed by change in lens thickness or refraction) indicates that the velocity of ciliary muscle contraction and changes in lens biometry increase, but without a further change in the lens dioptric power. A prior study has also shown a strong linear relationship between the peak velocity of an accommodative response and the amplitude.[32] The nonlinearity of the supramaximal stimulations observed in the current study shows that although the ciliary muscle and lens are capable of producing a faster accommodative response, it is without a further increase in accommodative amplitude. This suggests that, even in adolescent monkeys, the accommodative plant, rather than the brain, is the limiting factor in determining maximal accommodative amplitude, as it is in the presbyopic eye.[41,42] Supramaximal disaccommodative refractive and biometric responses (Figs. 7C, 7D) differ slightly, because biometry was recorded some time after refraction; and, although, by definition, the refractive responses to supramaximal stimulations were not greater in amplitude, the subsequently re-

TABLE 3. Lens Movements per Diopter of Accommodation with EW and Pharmacologically Stimulated Accommodation

Method	Anterior Lens Surface Movement	Posterior Lens Surface Movement	Center of Lens Movement	Increase in Lens Thickness
EW stimulation, max current	−0.044 ± 0.010	+0.022 ± 0.003	−0.011 ± 0.006	+0.067 ± 0.010
EW stimulation, supramax current	−0.044 ± 0.011	+0.025 ± 0.005	−0.009 ± 0.007	+0.069 ± 0.012
Carbachol stimulation at 30 minutes	−0.057 ± 0.009	−0.0017 ± 0.013	−0.029 ± 0.011	+0.055 ± 0.006

Lens surface movements per diopter of accommodation following maximal EW stimulation, supramaximal EW stimulation and pharmacological carbachol stimulation are shown. A negative value represents an anterior movement and a positive value represents a posterior movement. All values are mm/D ± SD.

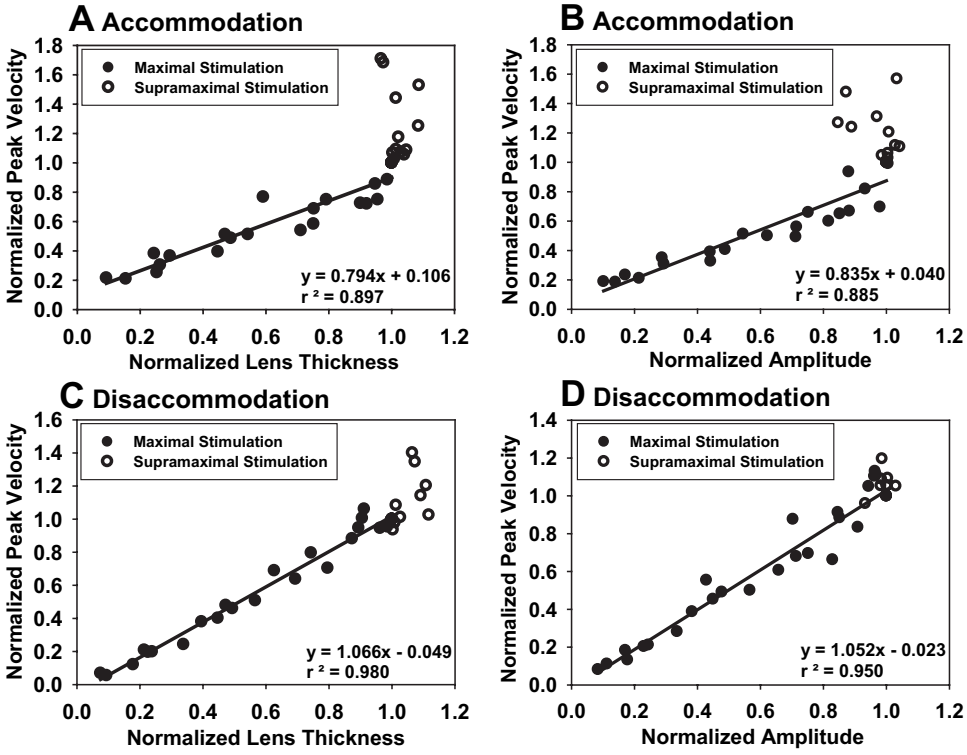

FIGURE 7. Peak velocity of (**A**) lens thickness and (**B**) refraction for accommodation for submaximal, maximal, and supramaximal EW stimulus current amplitudes. Peak velocity of (**C**) lens thickness and (**D**) refraction for disaccommodation for submaximal, maximal, and supramaximal EW stimulus current amplitudes.

corded biometric responses to the same stimulus amplitudes were slightly greater (this is also evident in the supramaximal stimulations in Fig. 3B). Nevertheless, the relationship between peak velocity of refraction and lens thickness for disaccommodation was linear for maximal and supramaximal EW stimulation. The differences in linearity between accommodation and disaccommodation suggest that, although accommodation is an active process occurring from a ciliary muscle contraction which can be increased in speed by increasing the stimulus current, disaccommodation is a passive process resulting from ciliary muscle relaxation and simply depends on the amplitude of the disaccommodative response.

The CUB measurements after carbachol iontophoresis require that the transducer remain in contact with the cornea throughout the 30-minute recording period. Therefore, refraction cannot be measured simultaneously. Transient corneal opacity due to prolonged exposure to the ultrasound transmission gel also precludes a refraction measurement at the end of the CUB biometry measurements. Instead, the maximal carbachol stimulated accommodative amplitudes were determined from two to five prior experiments in the same monkeys in which refraction was measured three times every 2 minutes for 30 minutes or longer after carbachol iontophoresis. In these experiments (Fig. 6A), the refractive change progresses steadily and systematically over time with no indication of any discontinuity or inflection point of the kind seen after the initial stage from the biometry. The accommodative refractive change should increase either through an increase in lens surface curvatures as is normally expected with accommodation or through an anterior movement of the lens. After EW stimulation, the lens thickness increased 0.067 to 0.069 mm/D. Based on the refractive and biometric amplitudes achieved from the independent carbachol experiments, at the end point of pharmacological stimulation, lens thickness would have increased 0.055 mm/D. Although this was not significantly different from the increase in lens thickness from EW stimulation, the slightly smaller increase in lens thickness per diopter suggests that the anterior movement of the fully accommodated lens with pharmacological stimulation may contribute to the increased refractive change relative to EW-stimulated accommodation.[29]

Carbachol iontophoresis delivers a high concentration of a powerful nonspecific muscarinic agonist directly to the anterior chamber of the eye. This may result in carbachol ultimately binding to and stimulating all postsynaptic neuromuscular receptors in the ciliary muscle. This may not represent a normal accommodative stimulus. Initially, after carbachol iontophoresis, the accommodative biometric changes are similar to the EW-stimulated biometric changes. Thus, even with supramaximal pharmacological stimulation, the lens initially undergoes a normal accommodative response. This progression from an initial normal accommodative response to a later forward shift of the lens would only be evident from having done dynamic or periodic recordings throughout the drug stimulated accommodative response. If the ocular biometry were only measured at a single, final time point (Findl O, et al. *IOVS* 2004;45:E-Abstract 1744)[25] the initial phase of the response would be missed.

EW-stimulated accommodation results from release of acetylcholine onto the ciliary muscle from the postganglionic parasympathetic neurons. This is similar to what occurs with visual stimulus-driven accommodation. These results show that the anterior movement of the posterior lens surface cannot be achieved with supramaximal EW stimulation. This finding indicates that an anterior movement of the posterior lens surface is not a normal component of visual stimulus-driven accommodation. In many studies of human accommodation, especially in presbyopes, pharmacological stimulation has been used to determine maximal accommodative amplitude.[14,15,17] For example, pilocarpine has been used to stimulate accommodation to evaluate the effectiveness of accommodative restorative procedures.[14,21,27] It is important to understand that the biometric changes during pharmacological stimulation may be different from that expected with visual stimulus-driven accommodation. Measuring ocular biometry at only one time point well after pharmacological stimulation may lead to erro-

neous conclusions about the pharmacologically stimulated biometric changes.

A previous study in rhesus monkeys measured biometric changes during EW- and pharmacologically stimulated accommodation with static A-scan biometry and Scheimpflug slit-lamp imaging and found similar lens movements with the two stimuli.[8] That study reported no movement of the posterior lens surface with accommodation. In the present study, using dynamic, high resolution A-scan biometry we found a systematic posterior shift of the posterior lens surface during EW-stimulated accommodation. This posterior movement of the posterior lens surface has been reported in humans during voluntary accommodation[5,10,25] and in rhesus monkeys during EW-stimulated accommodation.[12]

In the present study, the biometric changes in the initial phase after carbachol instillation were indistinguishable from those occurring with maximal EW-stimulated accommodation. In humans, it may be that with lower drug concentrations or at a sooner time point after pharmacological stimulation, the pharmacological and visual stimulus-driven accommodative responses are indistinguishable. If this is true, then pharmacological stimulation of accommodation would be useful to test the effectiveness of accommodative restorative procedures if measured at the appropriate time point after appropriate concentrations of drug instillation.

It is not clear why the lens undergoes an anterior shift with pharmacological stimulation of accommodation that is not seen with EW-stimulated accommodation in monkeys or visual stimulus-driven accommodation in humans. It is likely that most, if not all, of the ciliary muscle fibers are maximally contracted after supramaximal pharmacological stimulation. This may result in an anterior shift in the entire ciliary muscle that carries the lens or a greater release of zonular tension that allows the lens to shift anteriorly. Evidently, an anterior shift in the posterior lens surface is not a normal part of the accommodative process, but it can be made to occur with supramaximal pharmacological stimulation.

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