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Pharmacologically and Edinger–Westphal stimulated accommodation in rhesus monkeys does not rely on changes in anterior chamber pressure☆

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ABSTRACT

This study was undertaken to understand the role of anterior chamber pressure (ACP) during pharmacological and Edinger–Westphal (EW) stimulated accommodation in anesthetized monkeys. Experiments were performed on one iridectomized eye each of 7 anesthetized adolescent rhesus monkeys. Accommodation was induced by EW stimulation ($n = 2$) and intravenous administration of 0.25–4.0 mg/kg pilocarpine ($n = 6$). Accommodative refractive and biometric changes were measured with continuous 60 Hz infrared photorefraction ($n = 6$) and 100 Hz A-scan ultrasound biometry ($n = 1$). An ocular perfusion system was used to measure and manipulate ACP. Pressure was recorded via a 27-gauge needle in the anterior chamber connected to a pressure transducer ($n = 7$). The needle was also connected to a fluid reservoir to allow ACP to be manipulated and clamped ($n = 4$) by raising or lowering the fluid reservoir. In all six pharmacologically stimulated monkeys ACP increased during accommodation, from 0.70 to 2.38 mmHg, four of which showed pressure decreases preceding the pressure increases. Two eyes also showed increases in ACP during EW-stimulated accommodation of 2.8 and 7.2 mmHg. ACP increased with increasing EW stimulus amplitudes ($n = 2$). Clamping or externally manipulating ACP had no effect on resting refraction or on EW and pharmacologically stimulated accommodation in four eyes. The results show that EW stimulated and pharmacologically stimulated accommodation do not rely on ACP in rhesus monkeys.

1. Introduction

Intraocular pressure (IOP) has been suggested to play a role in the accommodative mechanism. The classical Helmholtz theory of accommodation states that ciliary muscle contraction releases zonular tension around the lens equator to allow the lens to become accommodated (Helmholtz von, 1962). Fincham proposed that the accommodative change in shape of the crystalline lens was caused by the elastic capsule molding the lens into an accommodated form (Fincham, 1937). Although the Helmholtz-Fincham capsular theory has been widely accepted, it has been challenged by an alternative IOP pressure based theory in which the zonular-lens diaphragm in each radial section is suggested to act as a catenary. In support of his theory, Coleman (Coleman, 1986) stated: "...differential pressure measurements between the vitreous and aqueous in primate eyes will be presented to document the existence of vitreous support during accommodation." – pg. 853. This theory suggests that a pressure differential between the anterior and vitreous chamber is produced by ciliary muscle contraction and acts on the catenary to cause the lens to become accommodated (Coleman, 1970, 1986; Coleman and Fish, 2001). Coleman (Coleman, 1986) shows pressure recordings from the anterior and vitreous chamber in primate eyes during ciliary muscle stimulation and states: "*In these tracings, an initial rise in vitreous pressure was simultaneously accompanied by a decrease in aqueous pressure. These amplitudes were typically quite small, averaging 4 cm of H_20 and accompanied by a strong piston-like forward movement of the lens similar to that described by Jampel and Mindel (Jampel and Mindel, 1967) with stimulation of the accommodative nucleus of the midbrain of the macaque.*" – *pg. 854*. The initial decrease in anterior chamber pressure (ACP) was suggested to be due to facilitation of aqueous outflow and the increase in vitreous chamber pressure was suggested to be due to ciliary muscle contraction (Coleman, 1986).

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If true, the catenary theory would challenge current understanding of the accommodative mechanism and many current approaches aimed at restoring accommodation to presbyopic eyes which rely on the elasticity of the lens capsule and not on changes in IOP (Glasser, 2006, 2008; Schor, 2009; Sheppard et al., 2010). Knowing if accommodation is affected by IOP would help to understand the accommodative mechanism and the accommodative forces that might be available to allow accommodation restoration strategies to succeed.

In a recent study, enucleated pig eyes were used to develop experimental methods to manipulate IOP (He et al., 2012b). Perfusion-induced pressure increases in the vitreous chamber of pig eyes caused a decrease in lens thickness which is opposite to the accommodative change predicted by the catenary theory. However, the absence of ciliary muscle contraction in enucleated pig eye means that the IOP changes do not necessarily emulate the pressure changes that might occur in a living primate eye with accommodation.

To study the relationship between accommodation and ACP, ideally either accommodation or ACP must be manipulated and the corresponding change in the other variable measured. Rhesus monkeys have an accommodative mechanism similar to humans (Glasser et al., 2006; Glasser and Kaufman, 1999) and a similar relative age-related progression of presbyopia to humans (Bito et al., 1982; Neider et al., 1990). Accommodation can be induced in monkeys by topically or systemically applied muscarinic agonists (Koretz et al., 1987; Ostrin and Glasser, 2007; Wendt and Glasser, 2010) or by Edinger–Westphal (EW) stimulation (Baumeister et al., 2008; Crawford et al., 1989; Vilupuru and Glasser, 2002). Intraocular pressure can be manipulated by changing the height of an ocular perfusion system reservoir (Ethier et al., 1993; He et al., 2012b; Kee et al., 1997). Ocular refractive or biometric changes can be dynamically measured during both accommodation and IOP manipulations (Beers and van der Heijde, 1994; Croft et al., 1998; He et al., 2012b; Ostrin et al., 2006; Vilupuru and Glasser, 2005). This study was undertaken to induce accommodation while manipulating ACP and measuring the ocular responses in rhesus monkeys to understand whether the changes in ACP during accommodation are causal or consequential.

2. Methods

2.1. Animal preparations

All experiments were performed in accordance with an institutionally approved animal protocol and conformed to the ARVO Statement for the Use of Animals of Ophthalmic and Visual Research. Seven adolescent rhesus monkeys, 8–13 years old, were used. Both eyes were previously iridectomized to allow photorefraction to be performed without interference from strong accommodation-induced pupil constriction (Kaufman and Lütjen-Drecoll, 1975; Vilupuru and Glasser, 2002). The iridectomy does not alter the accommodative response (Crawford et al., 1990b) or aqueous humor dynamics (Kaufman, 1979). Two of the monkeys, aged 9 and 13 years, had previously had stimulating electrodes surgically implanted in the EW nucleus of the midbrain (Baumeister et al., 2008; Crawford et al., 1989; Vilupuru and Glasser, 2002). For the experiments, the monkeys were initially anesthetized with intramuscular (i.m.) 15 mg/kg ketamine followed by intravenous (i.v.) propofol (PropoFlo, Abbott Laboratories, North Chicago, IL) with an initial bolus of 1.5 mg/kg and a continuous infusion at 0.5 mg/kg/min. Monkeys were wrapped in a 37 °C water heated pad, intubated and respirated. Pulse rate, SpO_2, and temperature were monitored. In some experiments, anesthesia was supplemented with 0.05 mg/kg i.m. medetomidine (Pfizer Inc., New York City, NY) and/or sutures were placed through medial and lateral rectus muscles to stabilize eye movements. Medetomidine was reversed with 0.25 mg/kg i.m. atipamezole (Pfizer Inc., New York City, NY) at the end of the experiments. For all experiments, the monkeys' head was positioned upright and facing forward in a head holder.

2.2. Sterilized perfusion system and pressure measurement

To allow manipulation and recording of anterior chamber pressure, a perfusion system similar to one described previously was developed and used (He et al., 2012b) (Fig. 1A and B). This consisted of a 5 cm internal diameter, 100 ml fluid reservoir with an outlet tube at the bottom connected to one opening on a 3-way stopcock. A second opening on the stopcock was connected via a plastic tube to a stainless-steel USB pressure transducer with a resolution of 0.00075 mmHg (PR41-X; Keller America Inc., Newport News, VA). The system was sterilized and filled with sterile heparinized Ringer's solution (1 unit/ml; Hospira, Inc., Lake Forest, IL) to prevent blockage. Any air bubbles present were dislodged to the open reservoir. The pressure transducer and the reservoir were each attached with clamps to two 50 cm long vertical posts marked at 2 cm intervals (corresponding to 1.5 mmHg in pressure). The height of the transducer was adjusted on the post to be at the same level as monkey eye.

A sterile 27 G butterfly needle (Becton–Dickinson, Franklin Lakes, NJ) with a short length of fine rubber tubing was attached to the third opening of the 3-way stopcock. Each needle was notched with a micro-file with three rings 1.5 mm from the tip to maintain the needle in the corneal stroma after insertion. Pressure was recorded using a custom Matlab (The Mathworks Inc., Natick, MA) program at 240 Hz. Immediately before the butterfly needle was inserted into the anterior chamber, the stopcock between the transducer and the needle was opened, the pressure transducer was set to the “default zero” factory calibrated zero pressure via the software. As a result, the pressure transducer generally recorded the absolute pressure based on its factory calibration. According to the manufacturer, the Keller pressure transducer has a resolution of 0.00075 mmHg and error range of ±0.075 mmHg. Pressure values, with the system times at which they were recorded, were written to a file once the pressure recording was started. The program also allowed the user to enter events during the experiment which were also recorded to the data file at the corresponding times.

Only one eye of each monkey was used, chosen randomly. The monkey eye lid was held open with a sterile speculum. The eye was viewed with a slit-lamp at high magnifications and the butterfly needle was inserted through clear cornea just anterior to the limbus so the beveled needle tip was completely in the anterior chamber on the temporal side. A custom made sterile, rigid contact lens with a notch 0.5 mm in width and 1.5 mm in length was placed on the cornea to fit around the needle to prevent corneal dehydration (Fig. 1C).

2.3. Pharmacologically and EW stimulated accommodation

Accommodation was stimulated with i.v. pilocarpine in six of the seven monkeys. As described previously (Wendt et al., 2013; Wendt and Glasser, 2010) following an i.m. protective dose of 0.05 mg/kg atropine (Phoenix Pharmaceutical, Inc., St. Louis, MO), several i.v. boluses of pilocarpine (Sigma–Aldrich Corp., St. Louis, MO) varying from 0.25 to 4.0 mg/kg were delivered over 30 s intervals at various times during the experiments using a syringe pump (KD Scientific Inc., Boston, MA). At the end of each i.v. pilocarpine experiment, a 0.5 mg/kg i.v. dose of atropine was given to reverse the effects of the pilocarpine. At the start of each i.v.

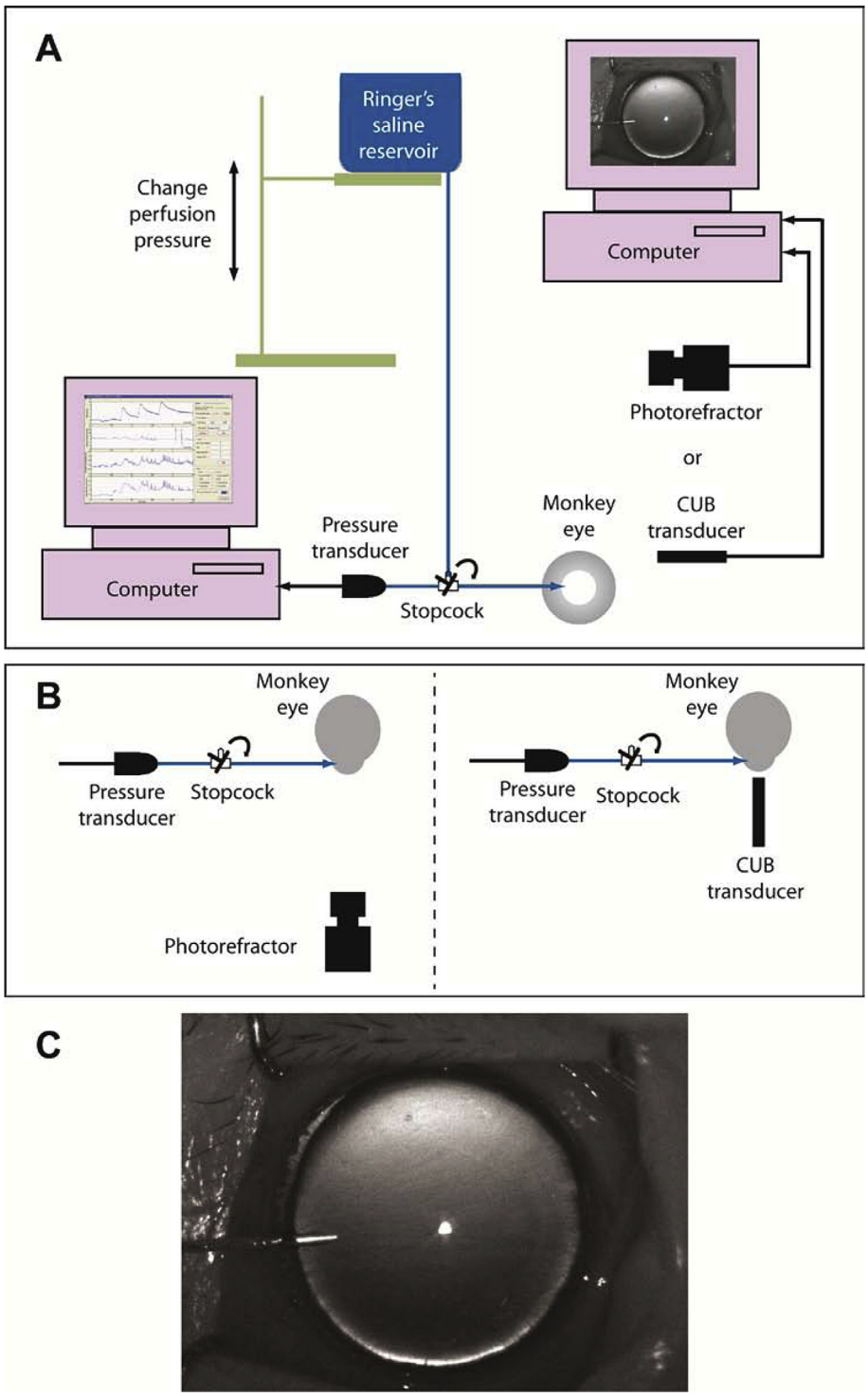

Fig. 1. (A) Diagram of the experimental system. One computer recorded anterior chamber pressure from a pressure transducer and the other computer recorded accommodative refractive change from the photorefractor or the axial biometric change from the continuous ultrasound biometer (CUB). Note that either the photorefractor or the CUB was used for the measurement, but not both of them at the same time. The pressure transducer was positioned at the same height as the eye. (B) As viewed from above, either the photorefractor (left image) or the CUB (right image) were aligned with the eye for accommodation measurements and the pressure transducer was off to the side. (C) Photorefraction image of a monkey eye (which is hyperopic relative to the photorefractor camera that is positioned 30 cm in front of the eye) with a 27-G needle in the anterior chamber through the temporal limbus with a notched contact lens on the cornea.

pilocarpine infusion, an event with the corresponding time stamp was written to the pressure recording file. These events were used to determine the starting time of all the pilocarpine stimulated pressure and accommodative responses.

Accommodation was induced with EW stimulation in two of the seven monkeys as described previously (Baumeister et al., 2008; Ostrin and Glasser, 2005; Vilupuru and Glasser, 2002). Stimulus pulse trains (frequency: 72 Hz; pulse width: 600 μs) 4-s in duration

were used with progressively increasing amplitudes from 0 μA to a current amplitude sufficient to produce maximum accommodation. For every stimulus amplitude, five consecutive stimulus trains were delivered each with 4-s long inter-stimulus intervals using a custom C++ program. The last three responses were averaged and baseline resting refraction was subtracted to calculate accommodative response in diopters. The program recorded the system times when the stimulus was delivered. These times were used to align the stimulus with accommodative response and the anterior chamber pressure recordings.

2.4. Accommodative refractive and biometric measurement

Accommodative refractive changes were measured with photorefraction as described previously (Baumeister et al., 2008; He et al., 2012a; Ostrin and Glasser, 2005; Vilupuru and Glasser, 2002). The photorefractor was mounted on a tripod 30 cm from the monkey eye. A custom developed C++ program captured the image (Fig. 1C) from the camera and performed real-time analysis at 60 Hz. The software located the first Purkinje image and calculated the averaged intensity gradient in a predetermined fixed 40% proportion of the entrance pupil aperture and fitted a linear regression line to the intensity gradient. The slope of the fitted line was converted to refraction by calibration with trial lenses (0 D to +10 D in 2 D steps) for each experiment (Choi et al., 2000; Vilupuru and Glasser, 2002). A recent study comparing maximal accommodation measured by Hartinger coincidence refractometer (HCR) and trial-lens calibrated photorefractor showed the difference was within 0.5 D (He et al., 2013). Baseline resting refraction was calculated by averaging the recording over the first minute prior to stimulation. Accommodation was calculated by subtracting the averaged baseline refraction from refractions over the whole time course of pilocarpine experiments. Because refraction continues to change after pilocarpine is administered (see results), the amplitude of each individual pilocarpine induced accommodative response was calculated by subtracting the initial refraction 10 s before each pilocarpine bolus from the peak refraction that occurred within 200 s after the pilocarpine bolus. The accommodative response for each individual EW stimulation was also calculated by subtracting average recordings over 1 s before every five stimulus trains from the raw refraction recordings. The position of the first Purkinje image was tracked by the software in pixels in x- and y- meridians as an indicator of horizontal and vertical eye movement. Times, photorefraction slopes, calibrated refraction values, horizontal and vertical Purkinje image positions were recorded to the photorefraction data files.

Since anterior chamber pressure was recorded with one computer and photorefraction was measured with another computer, an attempt was made to synchronize the system time on the two computers by updating both system time clocks with the atomic clock server at the National Institute of Standards and Technology (NIST). However, because of the long durations of the experiments and slightly different computer system clock speeds, this synchronization proved unreliable so precise synchronization between the timings of the accommodation recordings and the ACP recordings was not available. The maximal estimated synchronization error was about 2 s by the end of an experiment lasting several hours. The recorded responses from the two computers (IOP from one and photorefraction from the other) were visually aligned manually based on the manipulations performed when corresponding changes were recorded in both data files. This in general ensures the data can be aligned to within several data points (several milliseconds). Although this error is small compared to the time course for i.v. pilocarpine stimulation (30–40 s), it was not accurate enough to provide information on whether accommodation or ACP changed first.

In one monkey experiment in which both EW and pilocarpine stimulated accommodation were performed, axial accommodative ocular biometric changes including anterior chamber depth, lens thickness and vitreous chamber depth were measured with a custom built continuous A-scan ultrasound biometer (CUB) at 100 Hz (Baumeister et al., 2010; Beers and van der Heijde, 1996; Vilupuru and Glasser, 2005). Intravenous pilocarpine stimulation does not cause systematic eye movements, so this serves as a control in the same monkey for any possible influence on ACP of systematic convergence eye movements that may occur with EW stimulation. The CUB has a 10-MHz transducer with a 2 μm axial movement resolution (Beers and van der Heijde, 1994; Vilupuru and Glasser, 2005). The transducer was clamped in a micromanipulator (D-10 Positioner; Research Instruments, London, UK) in front of the eye. The transducer tip was placed in contact with a drop of ultrasound transmission gel (Liquasonic Ultrasound Gel; Chester Laboratories Inc., Cincinnati, OH) on the cornea and oriented to give sharp A-scan peaks for all ocular surfaces. The CUB records the time between the peaks and the times were converted to distances by multiplication with accepted sound velocities of 1532 m/s for the aqueous and vitreous and 1641 m/s for the lens (van der Heijde and Weber, 1989; Vilupuru and Glasser, 2005). Anterior chamber depth (ACD), lens thickness (LT), vitreous chamber depth (VCD) and ACP were recorded in real-time during accommodation stimulation and during ACP manipulation. Since the change in lens thickness and accommodation are linearly correlated (Vilupuru and Glasser, 2005), measurements of lens thickness by CUB can be used to indicate the accommodative response. In this experiment, ACP was increased, but not clamped, from the baseline pressure by up to 7.5 mmHg over 10–20 s using an infusion pump.

Table 1 summarizes the methods that were used to stimulate accommodation and to measure accommodative refractive/biometric changes.

2.5. Anterior chamber pressure manipulation

To control and clamp the anterior chamber to constant pressures, the reservoir was opened to both the anterior chamber and the pressure transducer via the 3-way stopcock and the height of the reservoir adjusted. Anterior chamber pressure was manipulated either by clamping at a constant level while accommodation was stimulated or by quickly raising or lowering the reservoir in steps.

3. Results

3.1. Pharmacologically stimulated accommodation

An example of an i.v. pilocarpine stimulated accommodation experiment is shown in Fig. 2. Refraction, ACP, horizontal eye

Table 1
Summary of methods that were used to stimulate accommodation and to measure accommodative refractive/biometric changes.

Animal ID	Accommodation stimulation	Accommodative measurement
38	i.v. pilocarpine	Photorefractor
119	i.v. pilocarpine	Photorefractor
73	i.v. pilocarpine	Photorefractor
50	i.v. pilocarpine	Photorefractor
70	i.v. pilocarpine	Photorefractor
58	i.v. pilocarpine	Photorefractor
	EW	Photorefractor
111	EW	CUB

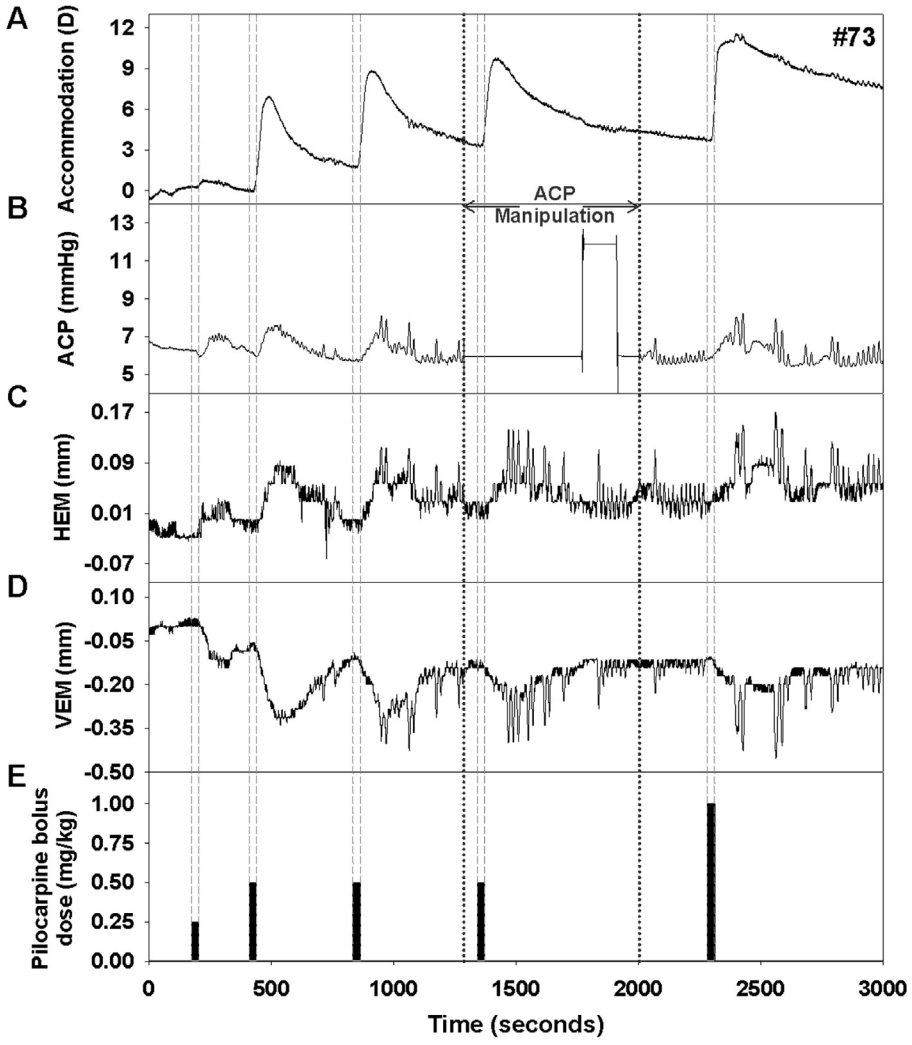

Fig. 2. An example from a pilocarpine stimulated accommodation experiment in monkey #73 showing (A) refraction, (B) anterior chamber pressure (ACP), (C) horizontal and (D) vertical eye movements (HEM and VEM) and (E) i.v. pilocarpine bolus dose as a function of time. ACP was clamped and then adjusted between the times of 1286 and 2004 s (dotted lines) during the experiment.

movement (HEM) and vertical eye movement (VEM) were recorded continuously. Between the times of 1286 and 2004 s, ACP was first clamped and then manipulated with a step increase. With the fifth i.v. pilocarpine bolus, maximum accommodation achieved was 11.90 D, with a local accommodative change of 7.91 D, and ACP increased by 2.36 mmHg (Table 2). Maximum accommodation and response duration increased progressively with increasing pilocarpine dose due to the cumulative effect of pilocarpine as described previously (Wendt and Glasser, 2010). Although accommodation increased progressively, ACP did not increase progressively with increasing accommodation. The first pilocarpine dose of 0.25 mg/kg resulted in a small accommodative response and a biphasic ACP change with an initial decrease of −0.34 mmHg and a subsequent increase of 0.92 mmHg (Table 2; Fig. 3D). Successive pilocarpine boluses from 0.50 mg/kg to 1.0 mg/kg caused similar changes in ACP of 2.38 mmHg and 2.36 mmHg. Although accommodation did not return to baseline with successive i.v. pilocarpine doses, the ACP did return to the same baseline or even lower towards the end of each response. Purkinje image recordings show that both the slow pressure drifts and the spikes in ACP

Table 2
Intravenous pilocarpine dose–response relationship in monkey #73 as shown in Fig. 2. Initial accommodation and ACP indicate the local values at the time each dose of pilocarpine was administered. Negative ACP amplitude means a pressure decrease while positive ACP amplitude means a pressure increase.

Pilocarpine dose (mg/kg)	Pressure manipulation	Initial Accomm. (D)	Max Accomm. (D)	Local Accomm. Response (D)	Initial ACP (mmHg)	ACP amplitude (mmHg)	
						Initial decrease	Later increase
0.25	No	0.23	0.81	0.58	6.26	−0.34	0.92
0.50	No	−0.05	6.96	7.02	6.27	−0.23	1.50
0.50	No	1.75	8.87	7.12	5.73	−0.07	2.38
0.50	Yes	3.35	9.80	6.45	5.96	0.00	0.00
1.0	No	3.69	11.60	7.91	5.81	−0.03	2.36

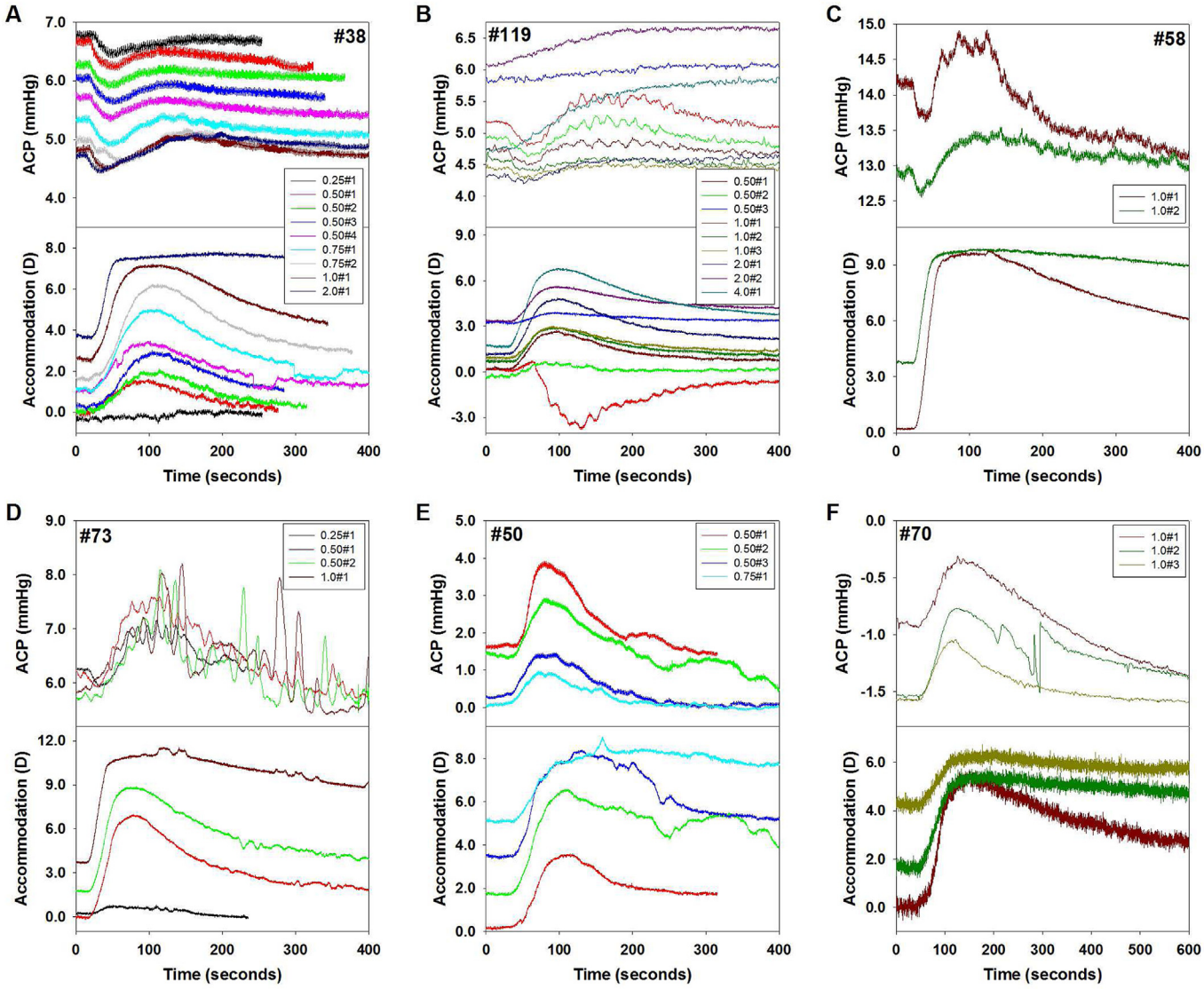

Fig. 3. (A–F) Pilocarpine stimulated accommodation relative to the pre-pilocarpine baselines (lower graphs) and ACP recordings (upper graphs) in six monkeys. All the ACP and accommodative responses were aligned with the time when the i.v. pilocarpine bolus was administered. Four of the six monkeys showed biphasic pressure changes (A–D). In the figure keys, the number before "#" indicates the pilocarpine bolus dose (mg/kg) and the number after "#" indicates the bolus number.

correspond with eye movements. Because of the needle in the anterior chamber, eye movements would be expected to induce pressure changes. However, in subsequent experiments, not all the ACP increases from all six monkeys were associated with eye movement. When ACP was clamped at 6 mmHg and the third 0.50 mg/kg pilocarpine bolus administered, a normal accommodative response occurred. During the ACP increase of 6 mmHg, no corresponding refractive change occurred. Table 2 shows that the calculated accommodative responses without and with pressure clamping were 8.87 D and 9.80 D with corresponding changes in ACP of 2.38 mmHg and 0 mmHg.

The results of similar i.v. pilocarpine stimulated accommodation experiments in six monkeys (including from monkey #73, shown above) are shown in Fig. 3. Successive responses start from increasing accommodated states because of the cumulative effect of successive i.v. pilocarpine doses as shown in Fig. 2. ACP amplitude for each single pilocarpine dose is defined as a local ACP change. Among all monkeys, maximum accommodation ranged from 6.7 D to 11.6 D and the ACP amplitude ranged from 0.70 mmHg to 2.38 mmHg. Four of the six monkeys showed pressure decreases below baseline pressure (A–D). In some cases these pressure decreases preceded a later pressure increase as reported previously (Coleman, 1986). There is a marked hyperopic refractive shift in one monkey (Fig. 3B) due to an oblique eye movement as determined from the movements of the first Purkinje image, although the corresponding ACP change was similar to those from the other accommodative responses. Baseline ACP before pilocarpine administration varied between eyes. This is likely in part due to intrinsic variations between monkeys and small but varied amounts of saline leakage from the needle or aqueous leakage from the eye when the needle was inserted into the anterior chamber. The only time that leakage was likely to have occurred would have been during the process of cannulation before the needle shaft sealed the insertion site. After the needle insertion, measured ACP was always stable, suggesting no further aqueous leakage. Fig. 3E shows a starting pressure close to zero while Fig. 3F shows a negative pressure of −0.5 to −1.5 mmHg. This negative pressure was possibly caused by the pressure transducer not being correctly

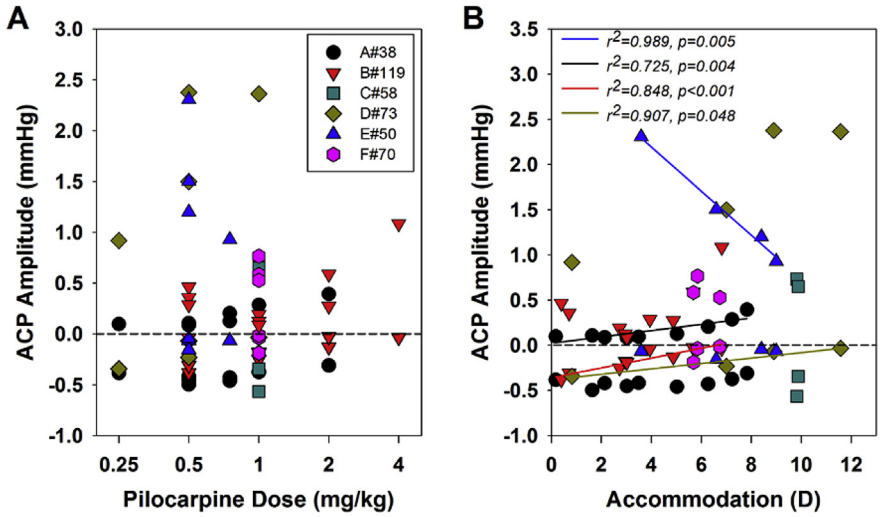

Fig. 4. ACP amplitude of initial decrease (negative) and successive increase (positive) as a function of pilocarpine bolus dose plotted on a logarithmic scale (A) and accommodation (B) in six monkeys. In B, linear regression lines were fit to the data from those monkeys in which ACP amplitude and accommodation show statistically significant correlations. In the figure key, the letter before "#" and the monkey ID after "#" correspond to the same monkeys as in Fig. 3.

zeroed prior to cannulation. Initial ACP may have affected the pattern of ACP change since monkeys #50 and #70 did not show initial pressure decreases and both had low ACP. However, in spite of differences in the pattern of ACP, these eyes all still showed normal accommodative responses.

ACP change was further studied as a function of pilocarpine dose and accommodative amplitude. Since in most cases ACP changes included an initial pressure decrease and later pressure increase, these two components were calculated and analyzed separately. ACP amplitude was calculated by subtracting the local pre-pilocarpine bolus baseline pressure from the extreme (maximum or minimum) ACP within 200 s after pilocarpine administration. A decrease in ACP was given a negative sign while an increase in ACP was given a positive sign. In some cases the ACP changes were close to zero (Fig. 3E and F). If the pressure change was biphasic, both negative and positive ACP amplitudes were extracted (Table 2). Fig. 4 shows ACP amplitude as a function of pilocarpine dose (Fig. 4A) and accommodation (Fig. 4B) from all six monkeys shown in Fig. 3. No systematic relationship exists for all eyes between ACP increase/decrease and accommodation (Fig. 4B). For four individual eyes that show significant relationships, three have a positive correlations and one a negative correlation (lines in Fig. 4B). The ACP decrease (negative amplitude), previously regarded as a necessary part of the pressure differential required to produce accommodation by the catenary theory, did not show any systematic relationships. In two eyes (inverted triangles and diamonds in Fig. 4B), in which ACP decrease showed a correlation with accommodation, the maximal accommodative response was achieved with an ACP change close to zero. In other words, no decrease in ACP occurred with maximum accommodation in these two eyes.

3.2. EW stimulated accommodation

Fig. 5 shows the data from EW stimulated accommodation in two monkeys in which accommodative refractive change was measured with photorefraction in one monkey (Fig. 5A upper graph) and the accommodative change in lens thickness (LT) was measured with the CUB in the other monkey (Fig. 5B upper graph). Accommodative increase in LT has previously been shown to be well correlated with the accommodative refractive response (Vilupuru and Glasser, 2005). In Fig. 5A upper graph, raw responses to three different stimulus amplitudes are shown. Although a sequence of five stimulations was used for each stimulus amplitude, only the last three responses of the sequence of five are

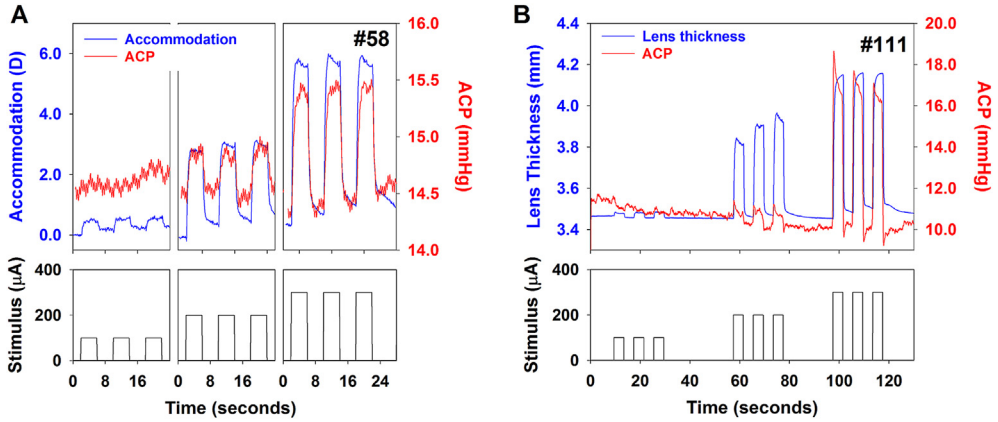

Fig. 5. The upper graphs are accommodation (left axis in A) and lens thickness (left axis in B) and ACP (right axis) during EW stimulation in two monkeys. The lower graphs show when the stimulus was on and off and indicate three different stimulus amplitudes.

shown. Fig. 5B shows a continuous raw recording in which only three stimuli were used for each of three different stimulus amplitudes. Both experiments showed increases in ACP of up to 2.8 mmHg (Fig. 5A) and 7.2 mmHg (Fig. 5B) during accommodation. The graphs demonstrate that the ACP changes occur coincident with the accommodative refractive (Fig. 5A) and biometric (Fig. 5B) changes with EW-stimulation, but they also show inconsistencies in amplitudes of accommodation and ACP thus demonstrating the lack of a causal relationship between change in ACP and accommodation.

Fig. 6A shows that accommodative response/lens thickness and ACP in general increased with increasing EW-stimulus amplitudes in the two monkeys shown in Fig. 5. However, the patterns of changes in accommodation and ACP were different from each other and inconsistent with the change in ACP. In Fig. 6A, for monkey #58, even though accommodation achieved an asymptote at a stimulus amplitude of around 400–450 μA, ACP was still increasing linearly. Similarly, for monkey #111, ACP changed differently from lens thickness with increased stimulus amplitude. No consistent relationship exists between either accommodation or change in lens thickness and ACP in the two monkeys (Fig. 6B).

3.3. *Pressure manipulation*

The results of pressure manipulations during EW stimulated accommodation in one monkey are shown in Fig. 7. In addition to recording normal ACP (~14 mmHg), ACP was also clamped at three different pressure levels (Low: 6 mmHg; Normal: 12 mmHg; High: 18 mmHg). Regardless of whether ACP was clamped or not or at what level it was clamped, the EW stimulated accommodative responses for each of the four different ACP conditions were similar (Fig. 7A). Fig. 7B shows the average accommodative response at each stimulus amplitude and demonstrates that the accommodative stimulus–response relationship was not affected by clamping the ACP at different levels.

Fig. 8 shows the effect of manipulating ACP on refraction. The decreasing accommodation in Fig. 8A, C and D was because these ACP manipulations were performed after the i.v. bolus pilocarpine doses started to wear off when accommodation was returning towards baseline. The pressure was manually changed by raising or lowering the reservoir. The manipulated pressure steps ranged from 3 to 9 mmHg but had no systematic effect on accommodation. In monkey #111, when ACP was increased by up to 7.5 mmHg this did not result in any corresponding changes in lens thickness or lens position within the eye (data not shown).

4. Discussion

The catenary theory suggests that a pressure differential produced by a decrease in ACP and an increase in vitreous chamber pressure molds the lens to take on a more spherical shape during accommodation (Coleman, 1969, 1970, 1986; Coleman and Fish, 2001). Two experimental findings have been suggested to support this. Ultrasound measurement of vitreous chamber depth during human voluntary accommodation was used to suggest that the posterior lens surface was supported by the vitreous (Coleman, 1970). However, several studies in humans (Beauchamp and Mitchell, 1985; Bolz et al., 2007; Dubbelman et al., 2005; Ostrin et al., 2006) and monkeys (Vilupuru and Glasser, 2005) show that the posterior lens surface moves backward during accommodation, and is therefore not supported by the vitreous as suggested by the catenary theory. This argues against vitreous support playing a role in producing the accommodative change in the lens. Other evidence suggested to support the catenary theory comes from IOP recordings during ciliary muscle stimulation in monkey eyes

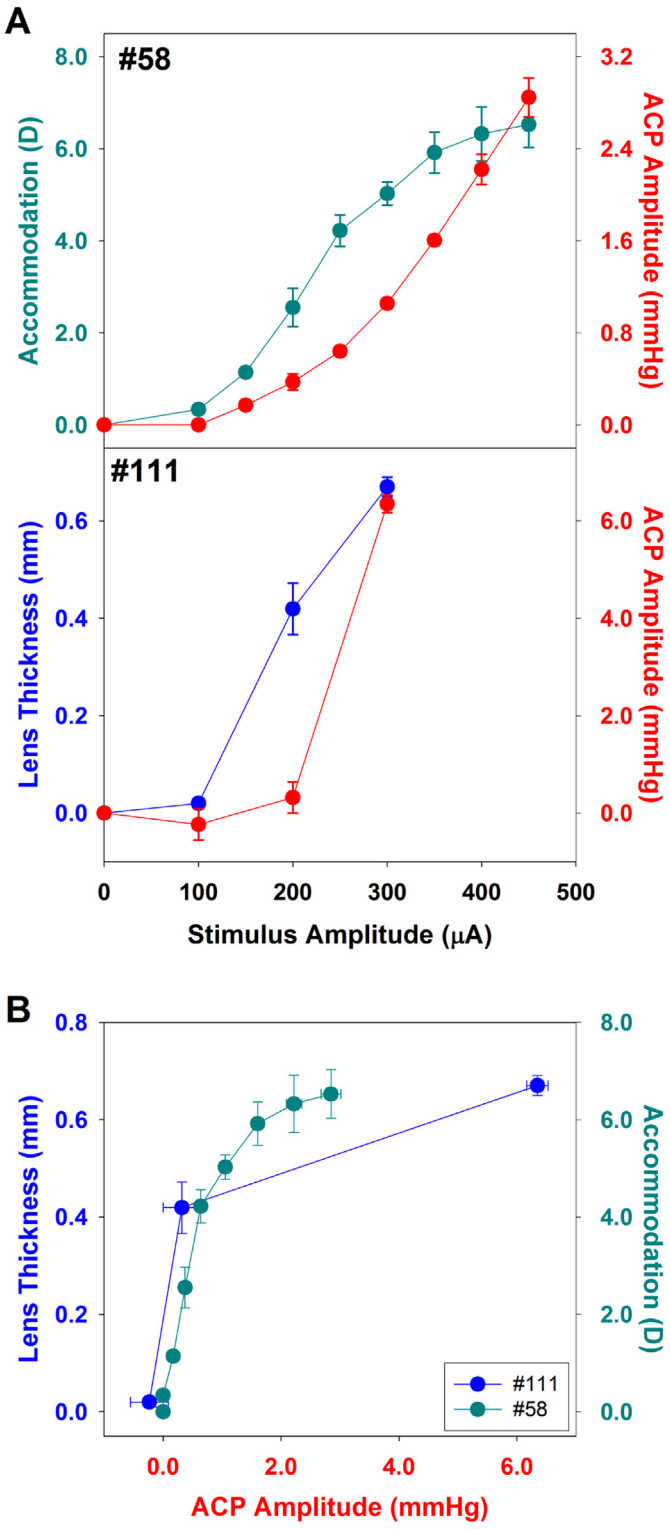

Fig. 6. Accommodation and ACP amplitude in two EW-stimulated monkeys. (A) The left *y*-axis corresponds to accommodation in diopters (green, upper graph) or lens thickness in mm (blue, lower graph) and the right *y*-axis shows ACP amplitude in mmHg (red). Both are plotted as a function of EW stimulus amplitude. (B) The lens thickness (left *y*-axis in blue) and accommodation (right *y*-axis in green) are plotted as a function of ACP amplitude (*x*-axis in red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

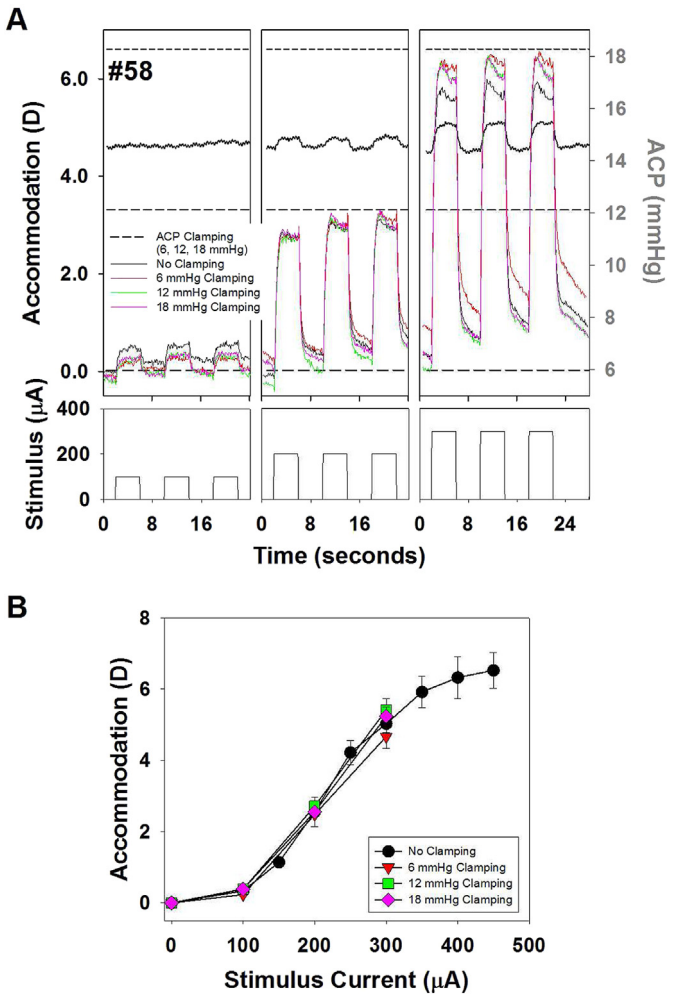

Fig. 7. (A) Four separate recordings of accommodation (upper graph, left axis) and ACP (upper graph, right axis) in response to three different stimulus amplitudes (lower graphs) in one monkey. The superimposed accommodative responses were recorded under four different conditions: without pressure clamping (black) and with pressure clamping at three levels: 6 mmHg (red), 12 (green) mmHg and 18 mmHg (pink). Unclamped ACP (black) increases between 14.5 and 15.5 mmHg (right axis) with each accommodative response. The black dashed lines are the ACP clamped at three different pressure levels and therefore were constant throughout the recordings. (B) Four different accommodative stimulus-response functions recorded under these four different ACP conditions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Coleman, 1986). These recordings showed an increase in vitreous chamber pressure that was suggested to be due to ciliary muscle contraction accompanied by an initial decrease in ACP that was suggested to be due to facilitation of aqueous outflow (Coleman, 1986). However, the decrease in ACP shown is small, brief and starts approximately 600 ms after the electrical stimulus to induce accommodation and lasts only 250 ms of the 1-s stimulus duration (He et al., 2012b). As shown in the current study, with both pharmacological and EW stimulation of accommodation, the accommodative responses and the changes in ACP are of similar durations. The ACP changes shown here are considerably longer and most are opposite in direction to the ACP decrease previously suggested to be a part of the pressure differential that caused the accommodative change in the lens (Coleman, 1986).

The results presented here demonstrate that the accommodative response is not dependent on ACP. The 2 mmHg decrease in ACP previously reported to be a part of the pressure differential that induced the accommodative change (Coleman, 1986) did not occur here in two monkey eyes with EW stimulated accommodation. Fig. 9 shows a comparison between EW stimulated ACP changes and ciliary muscle stimulated ACP changes digitized from the graph previously published with units converted from cm H_2O to mmHg by a factor of 1.36 (Coleman, 1986). The time course of three ACP responses at a stimulus current of 300 μA and duration of 4 s from Fig. 6A are normalized to a 1-s stimulus duration as used in the prior study (Coleman, 1986). The ACP recordings from the prior study and from the current study were aligned with the start of the stimulus. The sustained 1.06 ± 0.04 mmHg increase in ACP that occurs throughout the EW stimulus duration recorded in the current study is very different from the ACP change reported previously (Coleman, 1986). Of the six pharmacologically stimulated monkey eyes, four showed ACP decreases less than 0.5 mmHg and the overall ACP decrease was neither dependent on pilocarpine dose (Fig. 4A) or magnitude of pilocarpine-stimulated accommodation (Fig. 4B). For the individual eyes, two of the four eyes showed significant negative correlation between magnitude of initial ACP decrease and accommodation (inverted triangles and diamonds in Fig. 4B). This maximum accommodation was achieved when there was no initial ACP decrease or the ACP change was close to zero. According to the catenary theory, ciliary muscle contraction induced an initial decrease in ACP which plays a key role in producing the pressure differential, but since the decrease in ACP did not occur in every monkey or was negatively correlated with accommodation, or was modified by clamping (without an obvious change in accommodative response), a decrease in ACP is clearly not necessary for accommodation to occur.

Both pharmacologically stimulated and EW-stimulated accommodation suggest that ACP amplitude and accommodative responses are independent of each other. ACP amplitude was not significantly correlated with accommodation in all the monkeys. If changes in ACP were part of the pressure differential required to produce accommodation, ACP change would need to be highly reproducible to achieve highly reproducible accommodative responses. Although with EW stimulated accommodation, ACP increased with stimulus current, ACP continued to increase linearly even as the accommodative response plateaued (Fig. 6). This suggests that the stimulus is causing the ACP change independent of the accommodative response.

Clamping ACP during accommodation would modify any accommodative pressure differential (if it exists). However, clamping ACP did not alter the pharmacologically or EW stimulated accommodative responses. Step manipulation of ACP could also possibly produce a pressure differential and therefore induce a refractive change, but no refractive changes occurred when ACP was manipulated. Although vitreous pressure was not measured or manipulated in this study, clamping and step manipulations of ACP will certainly modify any pressure differential (if it exists). Clamping or manipulating ACP would profoundly alter the relationship between ACP and vitreous chamber pressure, therefore the normal pressure differential that is suggested to produce the accommodative response would be significantly altered by these manipulations. Both clamping and manipulating the ACP suggest that accommodation is independent of any pressure differential between the anterior and vitreous chambers of the eye.

Several other studies also provide evidence against the catenary theory. Fisher found no difference in subjectively measured accommodative response in a patient before and after vitrectomy (Fisher, 1982). Finite element analysis comparing the Helmholtz-Fincham capsular theory and Coleman's catenary theory show that the catenary theory produces less than half of the accommodative response of the Helmholtz-Fincham theory (Martin et al., 2005). In vitro mechanical stretching studies with enucleated and

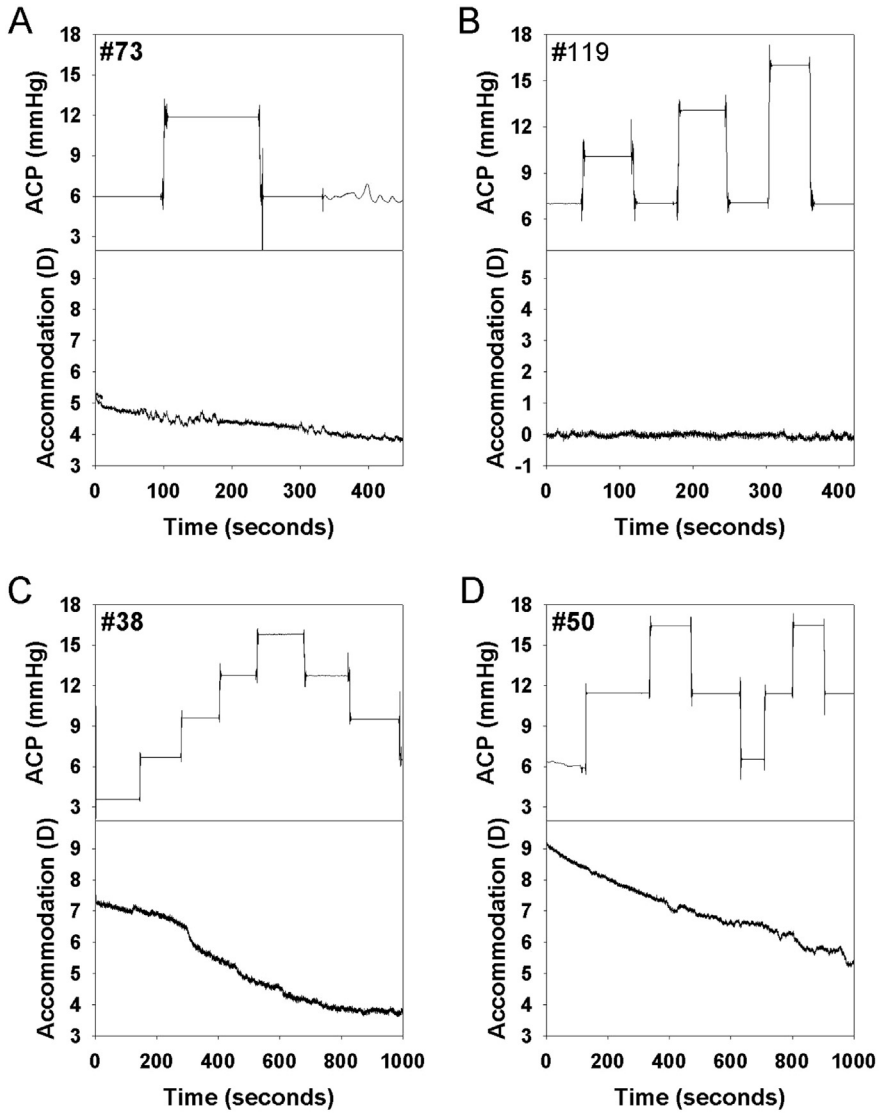

Fig. 8. Step manipulations of ACP (upper graphs) and corresponding refractive changes (lower graphs) from four monkeys. The slow drift in accommodation in (A), (C) and (D) was due to the eye recovering from the effect of a prior pilocarpine bolus while in (B) the pressure was manipulated before pilocarpine was administered and therefore the accommodation was stable around zero.

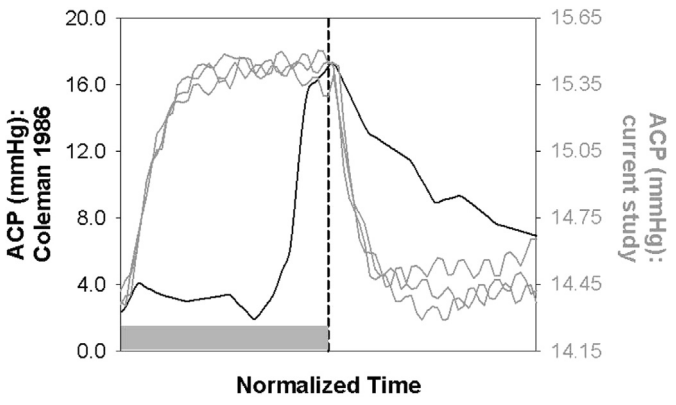

Fig. 9. A comparison of ACP change during EW stimulated accommodation in monkeys from the current study (gray lines) and a recording digitized from a prior study (black line) (Coleman, 1986). The stimulus duration was 4 s in the current study and 1 s the prior study (Coleman, 1986). To compare the time courses between the two studies, all the traces have time normalized to the duration of the stimulus used (gray horizontal bar). The dashed vertical line indicates the time at which the stimulus was terminated.

dissected human (Glasser and Campbell, 1998) and monkey eyes (Roorda and Glasser, 2004) in which the vitreous is completely removed and in which there can be no vitreous support or differential pressure changes show that normal accommodative changes still occur in the lens.

The cause of the recorded changes in ACP during accommodation is uncertain. Purkinje image tracking demonstrated that eye movement can cause increases in ACP (Fig. 2), although not all ACP changes were correlated with eye movements. Wandering eye movements can occur under propofol anesthesia (Glasser et al., 2006). EW stimulation can cause more rapid and larger eye movements than pharmacological stimulation (Glasser et al., 2006; Glasser and Kaufman, 1999) which could profoundly affect ACP. In general, eye movement can be minimized by stimulating accommodation through i.v. pilocarpine, by supplementing the anesthesia with medetomidine and by using extraocular muscle sutures to reduce eye movements. Although the eye movements may be reduced by sutures, eye movements could still cause changes in ACP as eye pulls against the sutures. Therefore, it is possible that some and/or part of changes in ACP are influenced by the eye

movement. Prior parasympathetic pathway accommodation stimulation studies in different animal species have also shown increases in ACP (Glasser et al., 1994; Hess, 1909; Jampel and Mindel, 1967; van Alphen, 1961). Since accommodation in some of these animals does not rely on changes in shape of the lens, this suggests that intraocular pressure changes may not be associated with accommodative changes in shape of the lens. The anterior lens surface moves forward into the anterior chamber during accommodation and the lens center moves forward a small amount (Vilupuru and Glasser, 2005). This could be the cause of the small increase in ACP that was observed in most of the experiments performed. The decreases in ACP recorded with i.v. pilocarpine stimulated accommodation could be associated with decreases in heart rate and blood pressure at the start of the i.v. pilocarpine infusions.

The anesthetic agents used in these experiments, ketamine and propofol, could potentially affect IOP and accommodation. Ketamine has been found to have varied effects on IOP and outflow facility among different species although studies in monkeys show that it does not significantly alter IOP in a single-day experiment (Bito et al., 1979; Erickson-Lamy et al., 1984). Propofol has been shown to cause an IOP reduction in pre-op patients which was thought to be related to an accompanying decrease in blood pressure (Neel et al., 1995). Anesthetic agents have also been shown to cause a myopic shift in monkeys, and monkeys have lower accommodative responses under Halothane vs Pentobarbital anesthesia (Crawford et al., 1990a). Repeated experiments in the same monkeys over time performed under ketamine or propofol anesthesia generally showed no differences due to the anesthetic agent used (Wendt and Glasser, 2012). The anesthetic agents used in these experiments are not likely to have any significant impact on the results obtained because the overall finding is that there is no influence of IOP on the accommodative response at least over the range of IOPs used for these experiments.

Although pharmacological stimulation of accommodation does not produce systematic eye movements, there are some drawbacks of pharmacological stimulation compared to EW stimulated accommodation for these experiments. Pharmacologically stimulated accommodation is relatively slow and takes even longer to return to baseline. Muscarinic agonists like pilocarpine can lower IOP by increasing outflow facility (Croft et al., 1996; Gabelt et al., 1991; Hubbard et al., 1996). This effect can result from ciliary muscle contraction which also happens during accommodation or from a direct action of the muscarinic agonist on receptors in the trabecular meshwork which may not occur during accommodation. Intravenous pilocarpine can produce systemic effects such as lowering blood pressure and heart rate (Tornqvist, 1967) which can influence IOP directly. Electrical stimulation of the parasympathetic pathway may also increase outflow facility, but this has been suggested to be due to ciliary muscle contraction (Armaly, 1959). The current results showed slight difference in the effects on ACP between these two accommodation stimulation methods. Pharmacological stimulation tended to produce an initial pressure decrease before a subsequent pressure increase while EW stimulated accommodation only produced an increase in ACP. Decreases in IOP after voluntary accommodation have been recorded with tonometry in humans (Armaly and Jepson, 1962; Blake et al., 1995; Cassidy et al., 1998; Jenssen and Krohn, 2012; Mauger et al., 1984; Read et al., 2010). All these studies measured IOP and all showed a decrease of 1–2 mmHg. Static recordings of a decrease in anterior chamber pressure do not identify if this pressure reduction is transient or constant. If transient, it might be due to a similar cause as the changes recorded here with pharmacologically stimulated accommodation.

The most appropriate method to measure ACP for these studies is through cannulation. Cannulation allows dynamic and simultaneous measurement of ACP and accommodation in the same eye. Although cannulation is invasive and the initial insertion of the needle might result in abnormally low baseline pressure (Fig. 3E and F), the current study was concerned with change in ACP during accommodation rather than with baseline ACP. Variation of the baseline pressure is not a confounding factor, because as Fig. 7 shows, when ACP was clamped at three different baseline pressure levels, EW-stimulated accommodative responses were almost identical. Therefore, baseline ACP does not affect accommodation.

In conclusion, although prior studies have suggested that a pressure differential caused by a decrease in ACP and an increase in vitreous chamber pressure occurs to mold the lens to produce accommodation, the accommodative refractive or biometric changes and ACP changes/manipulations reported here demonstrate that changes in ACP are not fundamental to the accommodative mechanism.

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