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Comparison of the ocular wavefront aberration between pharmacologically-induced and stimulus-driven accommodation

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Abstract

Purpose: To compare the ocular wavefront aberration between pharmacologically- and stimulus-driven accommodation in phakic eyes of young subjects.

Methods: The aberration structure of the tested eye when accommodating was measured using the Complete Ophthalmic Analysis System (COAS; AMO WaveFront Sciences, Albuquerque, NM, USA). It was used in conjunction with a purposely-modified Badal optometer to allow blur-driven accommodation to be stimulated by a high contrast letter E with a vergence range between +0.84 D and −8.00 D. Pharmacological accommodation was induced with one drop of pilocarpine 4%. Data from six subjects (age range: 23–36 years) with dark irides were collected.

Results: No correlation was found between the maximal levels of accommodative response achieved with an 8 D blur-driven stimulus and pharmacological stimulation. Pharmacological accommodation varied considerably among subjects: maximum accommodation, achieved within 38–85 min following application of pilocarpine, ranged from 2.7 D to 10.0 D. Furthermore, although the changes of spherical aberation and coma as a function of accommodation were indistinguishable between the two methods for low levels of response, a characteristic break in the pattern of aberration occurred at higher levels of pilocarpine-induced accommodation. This probably resulted from differences in the time course of biometric changes occuring with the two methods.

Conclusion: Measuring the pilocarpine-induced accommodative response at only one time point after its application may lead to misleading results. The considerable inter-individual differences in the time course of drug-induced accommodative response and its magnitude may lead to overestimation or underestimation of the corresponding amplitude of normal, blur-driven accommodation. Stimulating accommodation by topical application of pilocarpine is inappropriate for evaluating the efficacy of 'accommodating' IOLs.

Keywords: accommodation, crystalline lens, pilocarpine, spherical aberration, wavefront aberration

Introduction

Pilocarpine is a cholinomimetic alkaloid and is primarily a direct-acting parasympathomimetic agent that stimulates the muscarinic receptors present at the junction post-ganglionic parasympathetic nerves and their effector organs. When instilled into the conjunctival sac, pilocarpine acts as a muscarinic agonist and causes contraction of the smooth muscle of the iris sphincter and the ciliary muscle resulting, respectively, in pupillary miosis and lens accommodation (Vale and Cox, 1985), the dioptric change in the power of the crystalline lens offering optimal vision over a range of distances. Since pilocarpine stimulates ciliary muscle contraction, it has been therapeutically used for more than a century in the treatment of open-angle glaucoma, reducing intraocular pressure through the enhancement of aqueous outflow (Kanski, 1994).

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Pilocarpine drops have also been advocated clinically to induce miosis and control glare symptoms in patients who have undergone implantation of phakic intraocular lenses (IOLs) (Ellis, 2001; Maldonado *et al*., 2006) following cataract extraction. More recently, pilocarpine has been used in trials investigating the efficacy of 'pseudo-accommodating' IOLs in reversing presbyopia (Langenbucher *et al*., 2003; Findl *et al*., 2004; Koeppl *et al*., 2005b; Kriechbaum *et al*., 2005; Findl and Leydolt, 2007; Menapace *et al*., 2007). 'Accommodating' IOLs are supposed to partially restore accommodation of the human eye, through forward movement of the IOL optics mediated by a contraction of the ciliary muscle (Kuchle *et al*., 2002; Doane, 2004; Dick, 2005; Findl and Leydolt, 2007). It is now well established that the increase in axial thickness of the natural crystalline lens, as a result of ciliary muscle contraction when a young eye accommodates, is also accompanied by a forward movement of the lens surfaces, which results in a more powerful form (Koeppl *et al*., 2005a; Charman, 2008). Moreover, it has been shown that the ability of the muscle to contract remains almost intact throughout the lifespan (Glasser and Campbell, 1999; Pardue and Sivak, 2000). Pilocarpine is therefore used in pseudophakic eyes to pharmacologically stimulate muscle contraction, in order to objectively evaluate accommodative response. The use of objective methods in assessing the effectiveness of accommodative restoration procedures is essential, since the common subjective clinical measurement of the amplitude of accommodation often overestimates true accommodation, due to the increased depth-of-focus provided by small pupil size (Tucker and Rabie, 1980), or by corneal multifocality (Fukuyama *et al*., 1999), residual astigmatism (Huber, 1981) and higher-order ocular aberrations with larger pupils (Rocha *et al*., 2007). Objective methods have the further advantage that they do not necessitate active co-operation from the patient, which is a pre-requisite in voluntary blur-driven accommodation measurements.

However, there are certain drawbacks when pilocarpine is used as a stimulant. First, pilocarpine may result in an overestimation of accommodative response compared with physiologically-stimulated accommodation, especially in presbyopic phakic subjects (Koeppl *et al*., 2005a; Kriechbaum *et al*., 2005). Second, a considerable variability in the estimated amplitude of accommodation is observed between subjects (Berggren, 1985; Wold *et al*., 2003; Koeppl *et al*., 2005a), which is attributed to different responses to the drug, mainly because of iris colour (Glasser and Campbell, 1999; Wold *et al*., 2003). Significant inter-subject variance and greater levels of responses in drug-induced accommodation, compared to accommodation through stimulation of the Edinger–Westphal (EW) nucleus, have also been shown in monkey studies (Crawford *et al*., 1990; Neider *et al*., 1990; Ostrin and Glasser, 2005; Wendt *et al*., 2008). The variability of drug-induced amplitude of accommodation probably arises from changes in the thickness and the shape of the crystalline lens and in the anterior chamber depth (ACD) (Crawford *et al*., 1990; Ostrin and Glasser, 2005; Wendt *et al*., 2008).

Since visual stimulus- and pilocarpine-driven accommodation result in different physiological and anatomical changes in the anterior chamber depth (ACD) and crystalline lens biometry, it is expected that these differences would be reflected in the pattern of ocular wavefront aberration changes with accommodation. The aim of the present work is to monitor and compare the ocular wavefront aberration at different levels of accommodation stimulated by a blur-only stimulus and by pilocarpine instillation in young phakic subjects.

Materials and methods

Subjects

The dominant eyes of six subjects (four males, two females) with a mean age of 27 (range: 23–33 years) were tested. Five eyes were emmetropic, the other being low myopic corrected with (−1.75 D sphere) spectacles. Subjects had dark irides class D or E, according to the iris classification colour and pigmentation scale [see (Seddon *et al*., 1990)]. All subjects had a decimal visual acuity better than 1.0, normal binocular vision, phoria and near point of convergence, and no ocular pathology. None of the participants had a history of refractive or other ocular surgery. Verbal consent was obtained from all participants after they had received a written explanation of the nature of the study. The study was conducted in adherence to the tenets of the Declaration of Helsinki and followed a protocol approved by the University of Crete Research Board.

Wavefront sensing

The ocular wavefront error was measured using the Complete Ophthalmic Analysis System (COAS, AMO WaveFront Sciences Ltd). COAS technical specifications are described elsewhere (Plainis *et al*., 2005; Rozema *et al*., 2005). A purpose-built Badal optometer was mounted on top of the COAS sensor. Accommodation was controlled with a target viewed through a beam splitter, allowing for continuous recordings of the wavefront aberration of the tested eye. A wide range of target vergences between +1 D and −12 D was achieved without changing the apparent size of the target, thus inducing a blur-only stimulus for accommodation. The target was a high-contrast (>80%) single 6/126 letter E, printed on a white paper and

illuminated by an incandescent lamp (background luminance was 5 cd m^{-2}). Letter angular subtense was 1.75° (i.e. the limb widths subtended 21′ arc).

Experimental procedure: stimulus-driven wavefront sensing

The experiments were conducted on two consecutive days. On the first day ocular aberrations were evaluated under natural conditions for a range of target vergences. Room lights were dimmed to maintain large pupil diameters. Wavefront aberration data were initially recorded for positive target vergence (i.e., the target was placed behind the subject's far point at +0.84 D). In subsequent trials, the target was brought progressively closer to the subject to increase the stimulus vergence up to −8.05 D in about 1.00 D steps.

The subject positioned his/her head on the chin rest. Following careful alignment, 50 consecutive measurements were taken for each condition (with a duration of 6.5 s at a frequency of 7.7 Hz) for the full pupil without re-alignment being needed. The dominant eye was tested, the other being occluded. Subjects were asked to blink prior to all measurements. They were encouraged verbally to direct their attention to the target and maintain best possible focus at all times. A complete measurement session for each subject lasted about 30 min. Target vergence was corrected for effectivity for the spectacle-corrected participant, using *Equation 1*:

$$A = -L(1 + 2aK), \tag{1}$$

where A is the accommodation demand, L the target vergence, a the vertex distance (13 mm), and K the refractive power of the correcting lens.

Experimental procedure: pharmacologically-driven wavefront sensing

On the following day, pilocarpine-induced aberrations were assessed. With the Badal optometer turned off, wavefront aberration data of the dominant (tested) eye were initially recorded without administering any drug (baseline), with the fellow eye fixating on a letter placed at 4 m distance. Then, three drops of phenylephrine hydrochloride 10% (Cooper SA) were instilled to dilate, without cyclopleging, the measured eye. The first two were instilled at the same time, with the third following 15 min later, in order to fully dilate the pupils of the participants with dark coloured irides. A second wavefront measurement was taken 20 min after initial drug installation. Then, one drop of pilocarpine hydrochloride 4% (Isopto-carpine; Alcon Laboratories, Fort Worth, TX, USA) was instilled into the lower fornix of the measured eye. Wavefront recordings were performed about every 5 min for the first hour and every 10 min thereafter, until no difference was observed for two consecutive recordings.

Data analysis

The data extracted from COAS consist of a set of Zernike coefficients (up to fourth order) in Malacara format. The files containing wavefront information were downloaded on removable media and analyzed off-line using custom-written scripts in computational software (MATLAB V 5.2; The MathWorks Inc., Nantick, MA, USA). The Zernike expansion coefficients derived from the wave inclination data for the full pupil were initially transposed to the OSA format (recommended by the Optical Society of America; see Thibos *et al.*, 2000). They were also scaled to 3.5 mm pupil diameter and corrected for chromatic aberration (from 840 nm to 550 nm) as described elsewhere (Ginis *et al.*, 2004). Accommodative response for each recording, M, was evaluated from the second-order paraxial focus [c_2^0] and the fourth-order spherical aberration [c_4^0] Zernike coefficients (see *Equation 2*). This forms an approximation of equivalent spherical defocus used in common ophthalmic calculations and is found to be the most accurate method for predicting subjective refraction (Thibos *et al.*, 2004),

$$M = \frac{-c_2^0 4\sqrt{3} + c_4^0 12\sqrt{5}}{r^2}, \tag{2}$$

where M is in dioptres; the coefficients are measured in microns; and the pupil radius, r, in mm.

Results

Figure 1 presents typical records of accommodation response as a function of stimulus vergence for each participant. Each point of accommodation response was evaluated by the spherical equivalent of the wavefront aberration (see *Equation 2*) for a pupil diameter of 3.5 mm and corresponds to the mean of 50 consecutive wavefront recordings. It is apparent that all observers fail to accommodate accurately, exhibiting an accommodative 'lead' (over-accommodation) at low dioptric stimulus levels and an accommodative 'lag' (under-accommodation) at higher stimulus levels. Maximum accommodative lag (for the 8.05 D stimulus) ranged between subjects from 1.96 D to 2.90 D, whereas the accommodative lead, for a 0.15 D vergence target, ranged between subjects from 0.10 D to 1.56 D.

The effect of pilocarpine on pupil diameter and accommodative response as a function of time after instillation is depicted in *Figure 2*. *Figure 2a* shows plots of the pilocarpine-induced pupillary miosis. The pattern

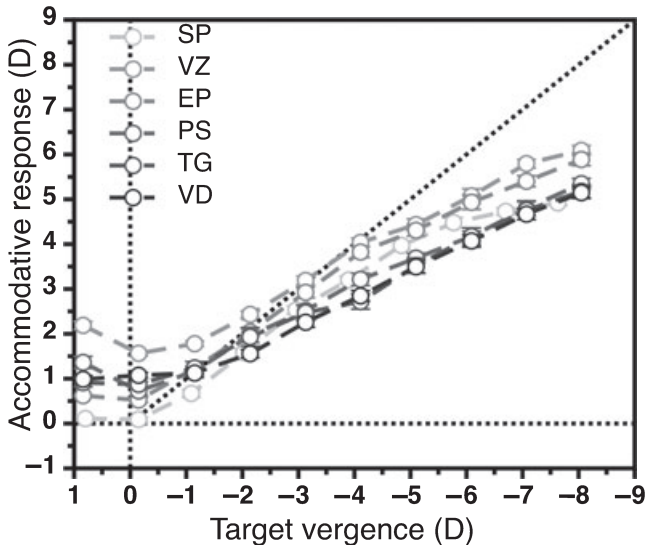

Figure 1. Stimulus-driven monocular accommodative response for a range of stimulus vergences, as calculated from the z_2^0 and z_4^0 Zernike coefficients of the wavefront aberration (see *Equation 2*) for each participant. Each data point represents the mean of 50 measurements and errors bars ±1 S.D. The dotted line is the ideal 1:1 relationship. Note that all subjects (except SP) exhibit an accommodative 'lag' for near targets and a 'lead' for far targets.

of the miotic effect is similar for all observers: pupil diameter reduces exponentially with time following pilocarpine instillation, reaching an asymptotic value after about 60–90 min. The average changes in normalised pupil diameter at 60 min and 90 min following pilocarpine instillation are 2.53 mm (range: 1.75–2.85 mm) and 2.74 mm (range: 2.45–3.18 mm) respectively. Note that pupil diameter at time zero was high for all subjects (> 6.00 mm), since phenylephrine drops were instilled about 20–25 min prior to pilocarpine application.

The changes in accommodative response following pilocarpine instillation are shown in *Figure 2b*. Although, it is evident that pharmacologically-induced accommodation increases approximately exponentially with time, there is a considerable variation among subjects both in the magnitude of the achieved response and in its dynamics. Specifically, the highest magnitude of the accommodative response varies between subjects from 2.7 D to 10.0 D, and the peak of the response is reached between 38 and 85 min following application of pilocarpine. Note that pilocarpine administration was repeated three times at different days for subject EP, who showed a low accommodative response on all occasions, and a consistently low maximal response (2.7, 2.6, 2.7 D). It should be emphasized that no correlation was found between the magnitude of blur-driven response for the highest dioptric stimulus and the maximum pilocarpine-induced accommodation (compare *Figures 1 and 2b*).

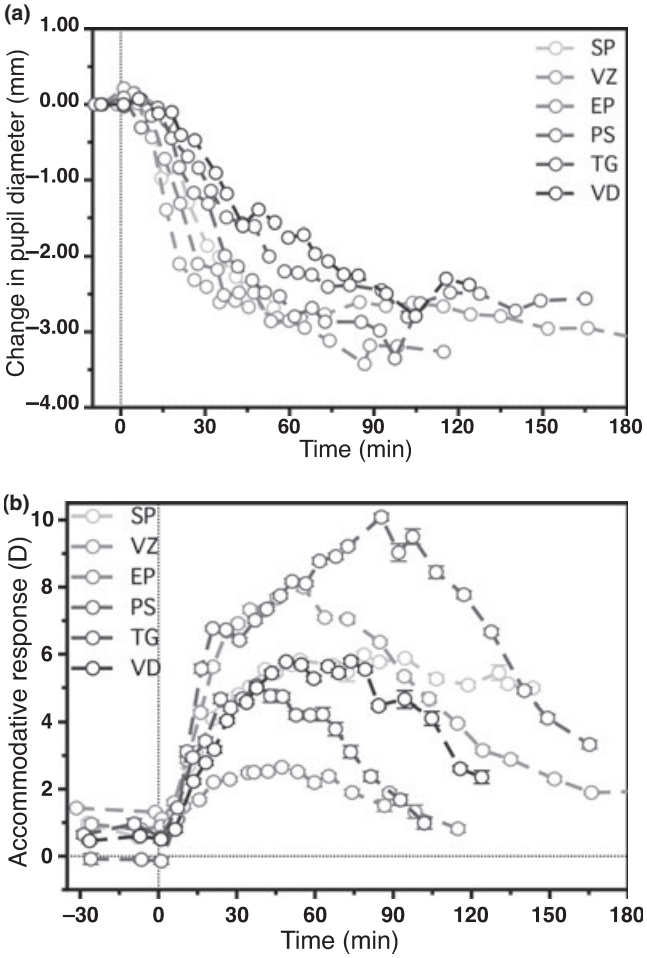

Figure 2. (a) Change in pupil diameter as a function of time following instillation (at time 0) of pilocarpine hydrochloride 4% for each observer. Note that three drops of phenylephrine hydrochloride 10% were instilled about 20–25 min prior to pilocarpine instillation in order to dilate, without cyclopleging, the pupils of the measured eye. (b) Pilocarpine-driven accommodative response, as a function of time following instillation (at time 0) of pilocarpine hydrochloride 4% in the measured eye for each observer.

The amount of pupil constriction per diopter of accommodation was determined by plotting pupil constriction, following pilocarpine instillation, vs the corresponding changes in accommodative response for each subject (see *Figure 3*). Straight lines were fitted to the linear portion of the pilocarpine-induced pupil vs. accommodation plots, i.e. including all points until the maximum accommodation response was achieved. The correlation coefficient, r^2, of the slopes of the linear regression was high for all subjects ($r^2 > 0.87$). As shown in *Figure 3*, although there is a systematic correlation between pilocarpine-induced miosis and accommodation, the amount of change in pupil diameter per dioptre change in accommodation response, varies substantially between subjects from 0.29 mm D^{-1} to 1.54 mm D^{-1}.

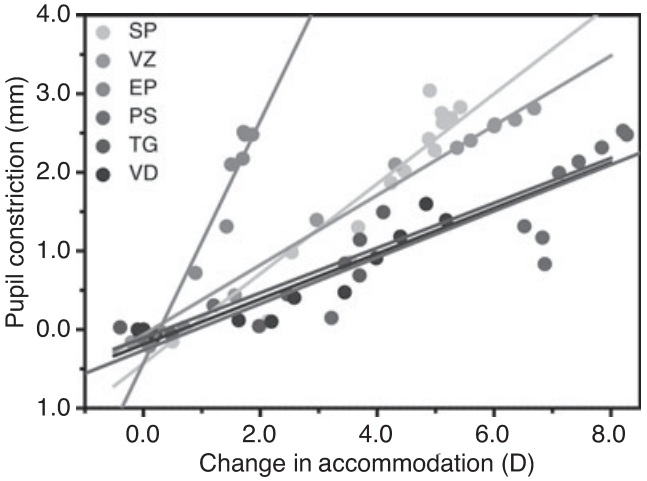

Figure 3. Plots of pupil constriction as a function of the corresponding change in accommodation response following instillation of pilocarpine hydrochloride 4% for all participants.

Figure 4 depicts the changes in two higher-order aberration terms, i.e. primary spherical aberration (c_4^0) and horizontal coma (c_3^{-1}), with physiologically- and pharmacologically-induced accommodation. The most systematic change occurs for spherical aberration (*Figure 4a*), which in the case of blur-induced accommodation always shifts towards more negative values with increasing accommodation level. The magnitude of the change in spherical aberration is linearly related to the accommodative response for all the subjects with the slope of the straight line fits ranging from 0.0067 μm D^{-1} to 0.0100 μm D^{-1} for a 3.5 mm pupil (the correlation coefficient, r^2, was higher than 0.90 in all cases). However, as shown in *Figure 4a*, the change of spherical aberration with pharmacologically-induced accommodation shows a biphasic pattern: spherical aberration moves to negative values for low levels of accommodation, in agreement with physiological

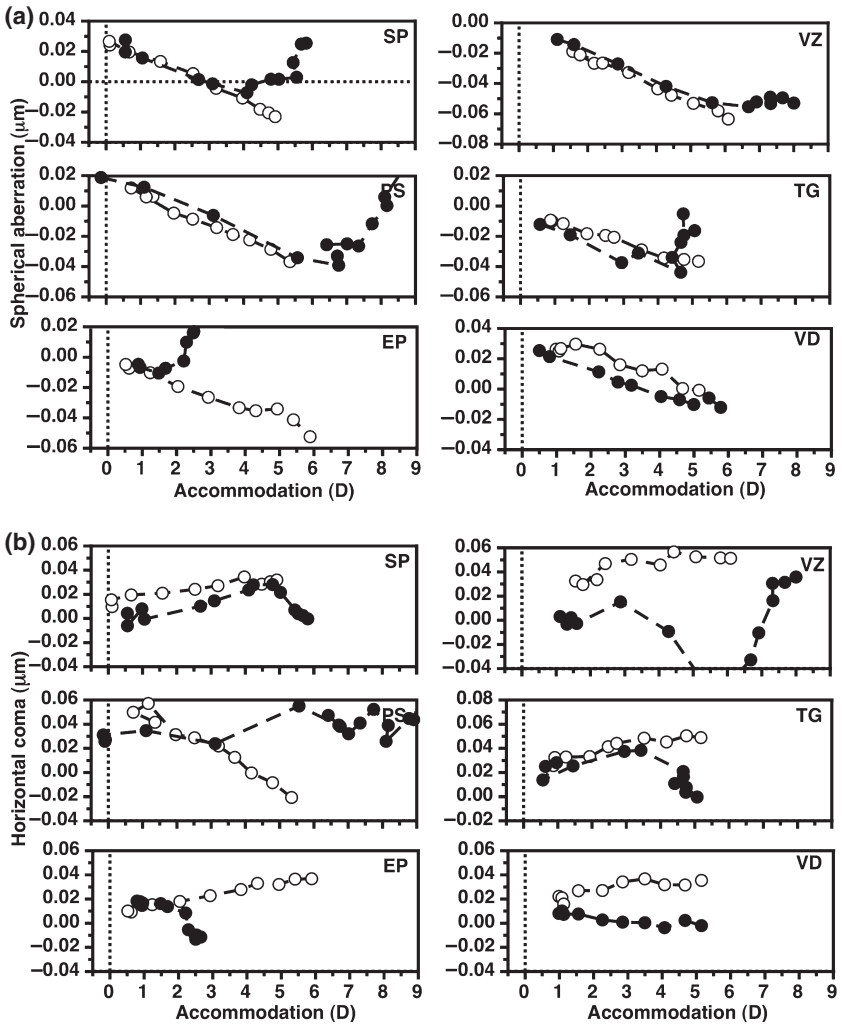

Figure 4. Plots of changes in the signed Zernike coefficients (μm) of spherical aberration (a) and horizontal coma (b) as a function of accommodative response for stimulus- (open circles) and pharmacologically- (filled circles) driven accommodative responses. Each data point represents the mean of 50 measurements. Analysis was performed for a 3.5 mm pupil diameter.

accommodation, but at a specific point a break appears in the slope with spherical aberration shifting towards more positive values. This break is a characteristic shared by most subjects and may occur at low (~1.5 D, see subject EP) or high (~7.0 D, see subject PS) levels of accommodation. It is absent only for one subject (subject VD).

Regarding the horizontal coma, c_3^{-1}, there is a tendency, with the exception of subject PS, for a change to more positive values with blur-induced accommodation (*Figure 4b*). The change in horizontal coma with pilocarpine–induced accommodation follows a similar pattern to spherical aberration, and tends to change direction at a higher accommodation level. Again, the break point is characteristic for each subject, corresponding closely with the break in spherical aberration vs. accommodation curve and ranging between 2 D and 6 D of accommodation.

In order to test if the break occurs at a specific time following parasympathomimetic activation, *Figure 5* plots the change in spherical aberration as a function of time following instillation of pilocarpine. The biphasic function is evident in all cases, with an exemption for subject VD. The break in the phases shows a significant inter-subject variability, occuring between 10 min to 25 min and is absent for subject VD.

Discussion

The results of this study indicate that the maximal blur-driven accommodative responses for an 8 D stimulus differ from those achieved with pharmacological stimulation. Although it is expected that the subjects could have reached higher responses for blur stimulus levels >8 D (see the stimulus/response curves in *Figure 1*), this does not affect the absence of any correlation found between the two methods. Blur-driven monocular accommodation confirms previous findings (Hazel *et al*., 2003; Radhakrishnan and Charman, 2007; Charman, 2008), producing higher errors in focus ('lags' of accommodation) for increasing dioptric stimulus levels, with their magnitude showing moderate variability between subjects, depending on factors that have been described elsewhere (Charman, 1995; Plainis *et al*., 2005).

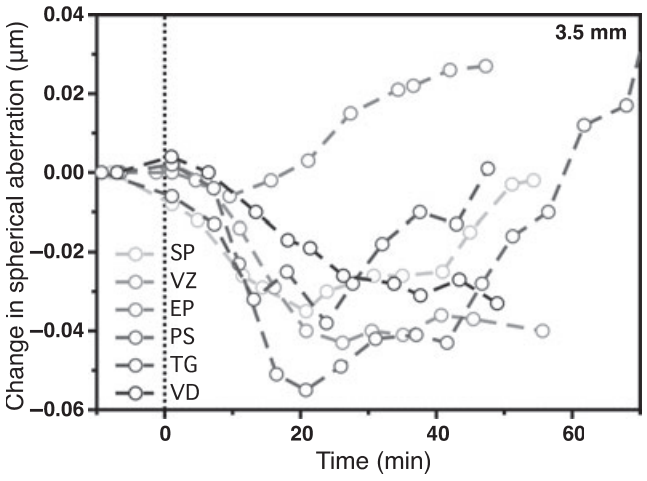

Figure 5. Plots of the change in spherical aberration (in μm) for all subjects as a function of time following instillation of pilocarpine hydrochloride 4%. Note that three drops of phenylephrine hydrochloride 10% were instilled about 20–25 min prior to pilocarpine instillation in order to dilate the pupil of the measured eye. Analysis was performed for a 3.5 mm pupil diameter.

On the other hand, instillation of one drop of pilocarpine 4% results in pronounced inter-individual but only small intra-individual differences in accommodative response, in agreement with other studies in humans (Berggren, 1985; Wold *et al*., 2003; Koeppl *et al*., 2005a) and monkeys (Crawford *et al*., 1990; Wendt *et al*., 2008). Moreover, although the mean accommodative amplitude stimulated by pilocarpine may not be significantly different compared to the mean stimulus-driven accommodation, as was also found for subjective methods (Wold *et al*., 2003), there is no correlation between the results derived by the two methods. Koeppl *et al*. (2005a) measured biometric changes in ACD and lens thickness induced both by pilocarpine and a near stimulus and claimed that pilocarpine acts 'physiologically' in young phakic subjects, producing a physiological maximal ciliary muscle constriction. However, their conclusion was based on comparison of mean values, while no correlation was found between accommodative amplitude and biometric lens changes.

It is well known that perception of an accommodative visual stimulus produces innervation of the ciliary muscle via the parasympathetic pathway (Toates, 1971; Stephens, 1985; Atchison, 1995). It has also been suggested that the sympathetic neurons of the ciliary muscle may result in a supplementary inhibitory response (Toates, 1971; Gilmartin, 1986). Ciliary muscle contraction and pupil constriction result from the release of the endogenous neurotransmitter acetylcholine at the ciliary neuromuscular junctions (Ostrin and Glasser, 2005), a pathway that is also shared in accommodation through stimulation of the Edinger–Westphal (EW) nucleus, which is the approach usually employed to induce accommodation in monkeys (Crawford *et al*., 1990; Ostrin and Glasser, 2005, 2007; Wendt *et al*., 2008). Pharmacological stimulation, on the other hand, delivers a muscarinic agonist, such as pilocarpine or carbachol, to the eye, which is diffused by the cholinergic receptors on the ciliary muscle, causing a progressive muscle contraction. It has been hypothesized that the different accommodative responses stimulated by pilocarpine as compared to those achieved by

voluntary accommodation to a visual stimulus may originate from the degree of implication of the iris sphicter muscle in the ciliary muscle contraction (Crawford *et al*., 1990). Crawford *et al*. (1990) compared carbachol-induced accommodation in the two eyes of unilaterally iridectomised rhesus monkeys and found a 40% reduction in accommodative amplitude in the aniridic eyes. They postulated that maximal drug-induced accommodation may be the result of the iris sphincter muscle pulling the ciliary body farther forward and inward, producing higher levels of accommodation.

The effect of pilocarpine on pupil diameter did not vary between subjects (see *Figure 2a*), but a considerable inter-subject variation in 'accommodative miosis' was observed (from 0.29 mm D^{-1} to 1.26 mm D^{-1}, see *Figure 3*), mainly due to the variability in the magnitude of pilocarpine-induced accommodation. In contrast, the substantial variation found in the degree of miosis induced by reflex and voluntary accommodation (Kasthurirangan and Glasser, 2006; Radhakrishnan and Charman, 2007) is mainly the result of pronounced differences in pupil contraction.

Since both visual stimulus-driven and pilocarpine-induced accommodation change the position and the radii of curvature of the lens anterior and posterior surfaces, it is not surprising to find changes in ocular wavefront aberrations. In agreement with previous studies (Ivanoff, 1956; Atchison *et al*., 1995; Cheng *et al*., 2004; Plainis *et al*., 2005), spherical aberration was found to move in the negative direction with increasing levels of blur-driven accommodation, becoming less positive/more negative. The changes in spherical aberration may be relevant to the changing second-order focus errors, i.e. lags of accommodation, with stimulus vergence (Plainis *et al*., 2005). Similarly, horizontal coma shows a tendency to change to more positive values. However, the change in aberrations following pilocarpine stimulation shows a bi-phasic pattern. This is evident both when aberrations are plotted as a function of the magnitude of accommodation (see *Figure 4a,b*) or the time course following pilocarpine application (see *Figure 5*).

The two phases in the plots denote that the biometric changes during pharmacological stimulation are different from those occurring with stimulus-driven accommodation. It is well established that, in a young eye, stimulus-driven accommodation increases the thickness and the shape of the crystalline lens to the more spherical lens form, with an increase in the anterior and posterior lens surface curvature. Moreover, the anterior lens pole moves forward, decreasing the ACD, while the posterior lens surface either does not move at all (Koeppl *et al*., 2005a), or shows a small posterior shift (Beauchamp and Mitchell, 1985; Langenbucher *et al*., 2003). Koeppl *et al*. (2005a) found that the biometric changes in young eyes 30 min following pilocarpine instillation are almost the same, with the only difference being a slight forward movement of the posterior lens pole, although the latter showed a high intra-subject variability. Changes in ACD have been shown to have an onset within 20 min and a peak in 60 min (Mehrotra *et al*., 1992). A recent study (Ostrin and Glasser, 2005), which compared dynamic EW-stimulated and pharmacologically-induced accommodation in monkeys, showed that the posterior lens surface shows a characteristic time course of biometric changes: initially it moves posteriorly, as is the case with voluntary accommodation, but within 2–10 min following application of carbachol the posterior lens surface starts moving anteriorly, the magnitude of the anterior shift varying between monkeys.

The biometric changes in the posterior lens pole after pharmacological stimulation, as discussed by Ostrin and Glasser (2005), may be the result of maximal contraction of ciliary muscle fibres, which does not occur with visually-driven accommodation. The bi-phasic pattern in the time course of wavefront ocular aberrations observed in this study corresponds well with the above biometric findings. The higher latencies in the break between the two phases compared to those found in monkey studies are likely to be due to the high intra-subject variability, the type of parasympathetic agonist used (pilocarpine vs carbachol) and any anatomical differences in the parasympathetic pathway between humans and monkeys.

Another interesting observation is that the spherical aberration changed sign at the higher drug-induced accommodation levels (see *Figure 4a*) while coma changed erratically (see *Figure 4b*). To change the spherical aberration, the lens surfaces presumably have to take a different shape (although the axial curvatures may be similar). It could be that pilocarpine affects the anterior parts of the ciliary body (and anterior lens fibres) to a different extent to the posterior parts. The resultant differences in the forces on the capsule might lead to different surface asphericities as compared to those for the normal accommodated lens. Similarly, any sectoral differences in the drug effect might result in slight variations in lens centration and tilt, and hence coma. This possibility is not unreasonable, since sectoral differences have been observed using Scheimpflug photography when the pupil was dilated pharmacologically (Chang *et al*., 1985).

It is therefore evident that measuring the pilocarpine-induced accommodative response and/or the corresponding biometric changes at only one time point after the drug application may lead to misleading results. Moreover, due to the considerable inter-individual differences in the time course of the accommodative response and its magnitude there is a strong possibility

of overestimating/underestimating blur-driven accommodation. Stimulation of accommodation by topical application of pilocarpine may therefore be inappropriate for evaluating the efficacy of 'accommodating' IOLs.

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