

Lag of accommodation predicts clinically significant change of spherical equivalents after cycloplegia

Cheng–Cheng Jin, Ru–Xia Pei, Bei Du, Gui–Hua Liu, Nan Jin, Lin Liu, Rui–Hua Wei

Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Branch of National Clinical Research Center for Ocular Disease, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin 300384, China

Correspondence to: Rui-Hua Wei. Fukang Rd. 251, Nankai District, Tianjin 300384, China. rwei@tmu.edu.cn

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Abstract

• **AIM:** To evaluate related factors with the change of spherical equivalents (Δ SE) and determine the suitable predictor of clinically significant Δ SE (≥ 0.50 D) with cyclopentolate hydrochloride on Chinese children.

• **METHODS:** A total of 145 right eyes of 145 children aged 4 to 15y were enrolled. Intraocular pressure, axial length and lag of accommodation (LOA) were assessed before cycloplegia induced by 3 drops of 1% cyclopentolate at 5-minute intervals. SE was measured before and 1h after the first drop of cyclopentolate. Δ SE was compared between different gender groups and among refractive groups. Multivariate linear regression analysis was performed to find related factors with Δ SE. ROC analysis was used to figure out the suitable predictor of clinically significant Δ SE.

• **RESULTS:** For the total 145 eyes, the mean SE reached up to -0.70 ± 1.86 D from -1.30 ± 1.62 D, with the mean Δ SE of 0.60 ± 0.55 D. The mean Δ SE were 0.63 ± 0.55 D and 0.57 ± 0.56 D respectively in the male and female group ($P=0.40$). The mean Δ SE was significantly different among different refractive groups ($P<0.0001$), with the Δ SE of hyperopia group (1.12 ± 0.64 D) larger than that of the emmetropia (0.56 ± 0.43 D, $P=0.001$) and myopia group (0.32 ± 0.28 D, $P<0.0001$). The Δ SE was correlated with LOA ($B=-0.54$, $P<0.0001$), cycloplegic SE ($B=0.10$, $P<0.0001$) and age ($B=-0.04$, $P=0.015$). ROC curve indicated that LOA predicted clinically significant Δ SE by 82% [area under the curve (AUC)=0.82] alone, while the value was slightly improved to 85% (AUC=0.85) in combination with axial length and 86% (AUC=0.86) in association with axial length as well as age.

• **CONCLUSION:** After cycloplegia with cyclopentolate, the Δ SE decreases with larger LOA, longer axial length and older

age. Specifically, LOA plays a more vital role in predicting clinically significant Δ SE.

• **KEYWORDS:** cycloplegia; cyclopentolate; spherical equivalent; clinically significant change; lag of accommodation

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INTRODUCTION

Adequate cycloplegia is of great importance for obtaining accurate refractive errors^[1-5], avoiding overestimation of myopia or underestimation of hyperopia especially for children at risk of myopia. Clinically, 1% cyclopentolate hydrochloride (cyclopentolate for short) is now being frequently applied to children because of its rapid onset and strong cycloplegic effect^[6-8].

However, the change of refractive errors was not clinically significant (less than 0.50 D) on some children after application of cyclopentolate, and they suffered from unnecessary side effects and spent much more waiting time. Although the changes of refractive errors after cycloplegia were found to be affected by various factors, previous studies have not found an ideal predictor of refractive changes^[9-11]. The cycloplegic refraction was found to be positively associated with the change of refractive errors^[9-11], but it could not play a predictive role because it was obtained after cycloplegia. Besides, intraocular pressure (IOP), age as well as living environment was also proved to be related with the change of refraction after cycloplegia, but the corresponding regression coefficients were less than 0.1^[11]. Therefore, it is vital to explore more predictive factors to help clinicians determine whether the use of cyclopentolate is necessary.

In this prospective study, our purpose was to evaluate related factors with the change of spherical equivalents (Δ SE) and to determine the suitable predictor of clinically significant Δ SE (≥ 0.50 D) after application of 1.0% cyclopentolate hydrochloride to Chinese children. The results may help to reduce the waste of medical resources, promote the efficiency of diagnosis as well as improve the patient's medical experience.

SUBJECTS AND METHODS

Ethical Approval Informed consent in written form was signed by patients and their legal guardians. The study followed the Declaration of Helsinki and was approved by the Tianjin Medical University Eye Hospital Medical Ethics Committee.

Inclusion Criteria Chinese children with dark irises aged from 4 to 15y were randomly selected from the Optometry Clinic of Tianjin Medical University Eye Hospital from September 2019 to October 2019.

Exclusion Criteria Subjects with over 1.50 D (including 1.50 D) of astigmatism, manifest strabismus, amblyopia, nystagmus, media opacity including congenital cataract, glaucoma or an IOP higher than 25 mm Hg in either eye, history of ocular surgery or trauma, history of wearing contact lens including orthokeratology lens, history of drugs affecting accommodation such as atropine with low concentration and poor cooperation were excluded from the study.

Examinations All subjects went through general ophthalmologic examinations including non-contact tonometry (computerized tonometer, CT-1, Topcon Co., Tokyo, Japan), measurement of axial length (AL; Biometer, LS-900, Haag-Streit AG Co., Switzerland), non-cycloplegic autorefraction (autorefractor, KR-800, Topcon Co., Tokyo, Japan), assessment of lag of accommodation (LOA; binocular autorefractor/keratometer, WR-5100K, Grand Seiko Co., Ltd., Hiroshima, Japan) and evaluation of eye health (slit-lamp assisted biomicroscope, YZ5F1, Weihai Dingxin Optical Co., Ltd., China) before cycloplegia. Cycloplegia was induced by instilling three drops of 1% cyclopentolate (Cyclogyl[®], Alcon[®], <https://www.alcon.com/>) at 5-minute interval after topical anesthesia with one drop of 0.4% oxybuprocaine hydrochloride (Benoxil[®], Santen[®], <https://www.santen.com/en/>). The drug was carefully instilled into the conjunctival sac in order to avoid irritating tearing which may affect the effect of cycloplegia. Then, in order to reduce systemic absorption and loss of eye drops, participants were told to raise their heads and close the eyes gently with punctual occlusion using sterile cotton buds. Cycloplegic autorefraction was performed 1h after the first drop of cyclopentolate.

LOA was measured by the open-field binocular autorefractor before cycloplegia. Wearing the trial framework with the retinoscopy refractive correction, subjects with left eyes occluded were instructed to view at the 20/100 Snellen letter at a distance of 33 cm and keep it clear. Five readings were acquired each time and the average SE was recorded as the accommodative response when the difference between the maximum and the minimum was less than 0.25 D. Otherwise, the examination was repeated. LOA was calculated by accommodative stimulus (3.00 D) minus accommodative response.

Table 1 Demographic characteristics and ocular parameters of the 145 enrolled participants

Parameters	Mean±SD or ratio	95%CI
Gender ratio (M/F)	82/63	NA
Age (y)	9.1±2.4	8.7 to 9.5
IOP (mm Hg)	17.5±2.4	17.1 to 17.9
LOA (D)	+1.13±0.46	+1.05 to +1.20
AL (mm)	23.55±1.03	23.38 to 23.72
Cycloplegic SE (D)	-0.70±1.86	-1.00 to -0.39

IOP: Intraocular pressure; LOA: Lag of accommodation; D: Diopter; AL: Axial length; SE: Spherical equivalent.

SE were obtained according to the results of autorefraction measured by the Topcon KR-800 autorefractor. The measurements of SE were both repeated at least three times until the difference between any two measurements was no more than 0.25 D. The average was recorded and included in the analysis.

Definitions The refractive errors obtained from the autorefractor were decomposed into three components: sphere (S), cylinder (C) and axis (A). SE was calculated according to the formula: $SE = S + C/2$. In this study, cycloplegic $SE < -0.50$ D was defined as myopia, with cycloplegic $SE > +0.50$ D defined as hyperopia and the rest defined as emmetropia. Besides, ΔSE was calculated by subtracting noncycloplegic SE from cycloplegic SE. Clinically significant ΔSE was defined as the situation when ΔSE was not less than 0.50 D.

Statistic Analysis Only the data from right eyes were included for analysis. One-way ANOVA or Kruskal-Wallis test was used to compare the mean ΔSE and relevant parameters among different refractive groups. Independent samples *t*-test or Mann-Whitney *U* test was carried out to compare the mean ΔSE and relevant parameters between different sex groups. Spearman correlation analysis and multivariate linear regression analysis were conducted to determine the associated factors of ΔSE . Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) among different models were compared to detect the ability of LOA to predict clinically significant ΔSE (≥ 0.50 D) alone and in association with AL and age. All the statistical analyses were completed in IBM SPSS statistics version 23.0 (IBM Co., Armonk, NY, USA) and two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patient Information A total of 145 children (82 males, 63 females) were eventually enrolled with an average age of 9.1±2.4 (range: 4 to 15)y. The demographic characteristics and ocular biological parameters of the 145 enrolled participants were shown in Table 1. The whole sample was composed of 67 myopia (46%), 38 emmetropia (26%) and 40 hyperopia (28%).

Table 2 Comparison of mean ΔSE and related parameters among different refractive groups

n=145

Parameters	Myopia (n=67)	Emmetropia (n=38)	Hyperopia (n=40)	Statistic	P
Gender ratio (M:F)	33:34	25:13	24:16	2.97 ^a	0.23
Age (y)	9.8±2.3	9.4±2.5	7.8±2.1 ^c	9.53 ^b	<0.0001
IOP (mm Hg)	18.1±2.5 ^f	17.0±2.2 ^f	17.2±2.2	3.51 ^b	0.032
LOA (D)	+1.28±0.46	+1.12±0.42	+0.88±0.41 ^c	10.64 ^b	<0.0001
AL (mm)	24.21±0.94 ^e	23.29±0.62 ^e	22.69±0.73 ^e	46.76 ^b	<0.0001
Cycloplegic SE (D)	-2.25±1.43 ^e	-0.08±0.26 ^e	+1.31±0.73 ^e	124.28 ^c	<0.0001
ΔSE (D)	0.32±0.28 ^e	0.56±0.43 ^e	1.12±0.64 ^e	29.15 ^d	<0.0001

^aChi-square test; ^bOne-way ANOVA with LSD post-hoc test; ^cKruskal-Wallis test; ^dWelch's ANOVA with Games-Howell post-hoc test; ^eSignificantly different from other groups ($P<0.05$); ^fSignificantly different between two groups ($P<0.05$). IOP: Intraocular pressure; LOA: Lag of accommodation; D: Diopter; AL: Axial length; SE: Spherical equivalent; ΔSE: Change of spherical equivalent after cycloplegia with 1% cyclopentolate.

Subgroup Analysis of ΔSE For the whole 145 participants, the mean SE increased to -0.70 ± 1.86 (range: -6.25 to $+3.63$) D from -1.30 ± 1.62 (range: -6.25 to $+2.63$) D during 1h. The mean ΔSE was 0.60 ± 0.55 (range: -0.25 to $+2.38$) D. The mean ΔSE was significantly different among different refractive groups (Welch's ANOVA, $F_{2,65,11}=29.15$, $P<0.0001$, Table 2). The mean ΔSE of hyperopia group (1.12 ± 0.64 D) was significantly larger than that of emmetropia group (0.56 ± 0.43 D; Games-Howell post-hoc test, $P<0.0001$) and myopia group (0.32 ± 0.28 D; Games-Howell post-hoc test, $P<0.0001$). However, the mean ΔSE showed no significant difference (Mann-Whitney *U* test, $Z=0.84$, $P=0.40$, Table 3) between the male group (0.63 ± 0.55 D) and the female group (0.57 ± 0.56 D).

Factors Associated with ΔSE In univariate analysis, Spearman correlation analysis revealed that the ΔSE increased significantly with less LOA ($r=-0.59$, $P<0.0001$; Figure 1A), younger age ($r=-0.37$, $P<0.0001$; Figure 1B), shorter AL ($r=-0.36$, $P<0.0001$; Figure 1C), lower IOP ($r=-0.29$, $P=0.0001$; Figure 1D), more hyperopic cycloplegic SE ($r=0.58$, $P<0.0001$; Figure 1E) and more hyperopic initial SE ($r=0.29$, $P<0.0001$; Figure 1F). However, the ΔSE was not significantly correlated with gender ($r=0.070$, $P=0.40$). In multivariate analysis, because of strong collinearity of cycloplegic SE (variance inflation factor: 12.25) and initial SE (variance inflation factor: 12.25) when they were included in the same model, we analyzed the correlated factors found in the univariate analysis in two models including cycloplegic SE or initial SE, respectively. When initial SE was enrolled (Table 4), multivariate linear regression indicated that higher ΔSE was associated with less LOA ($B=-0.63$; 95%CI: -0.78 , -0.48 ; $P<0.0001$), shorter AL ($B=-0.10$; 95%CI: -0.18 , -0.03 ; $P=0.007$) and younger age ($B=-0.04$; 95%CI: -0.07 , -0.01 ; $P=0.015$). However, IOP ($P=0.21$) and initial SE ($P=0.67$) were no longer significantly correlated with ΔSE. When cycloplegic SE was enrolled (Table 5), multivariate linear regression revealed that higher ΔSE was associated with

Table 3 Comparison of mean ΔSE and related parameters between different gender groups

n=145

Parameters	Male (n=82)	Female (n=63)	Statistic	P
Age (y)	9.2±2.5	9.1±2.4	0.25 ^a	0.80
IOP (mm Hg)	17.4±2.3	17.8±2.4	-1.03 ^a	0.30
LOA (D)	+1.14±0.46	+1.11±0.46	0.44 ^a	0.66
AL (mm)	23.68±1.08	23.39±0.95	1.69 ^a	0.09
Cycloplegic SE (D)	-0.57±1.96	-0.87±1.71	1.43 ^b	0.15
ΔSE (D)	0.63±0.55	0.57±0.56	0.84 ^b	0.40

^aIndependent-samples *t*-test; ^bMann-Whitney *U* test; IOP: Intraocular pressure; LOA: Lag of accommodation; D: Diopter; AL: Axial length; SE: Spherical equivalent; ΔSE: Change of spherical equivalent after cycloplegia with 1% cyclopentolate.

Table 4 Multiple linear regression analysis of association between ΔSE and potential associated factors including initial SE

n=145

Factor	β	B	95%CI	t	P	VIF
LOA	-0.53	-0.63	-0.78, -0.48	-8.26	<0.0001	1.05
AL	-0.19	-0.10	-0.18, -0.03	-2.72	0.007	1.30
Age	-0.18	-0.04	-0.07, -0.01	-2.46	0.015	1.30
IOP	NA	NA	NA	-1.26	0.21	1.14
Initial SE	NA	NA	NA	-0.43	0.67	2.13

ΔSE: Change of spherical equivalent after cycloplegia with cyclopentolate; β : Standardized correlation coefficient; B: Regression coefficient; VIF: Variance inflation factor; LOA: Lag of accommodation; AL: Axial length; IOP: Intraocular pressure; SE: Spherical equivalent.

less LOA ($B=-0.54$; 95%CI: -0.69 , -0.38 ; $P<0.0001$), more hyperopic cycloplegic SE ($B=0.10$; 95%CI: 0.06 , 0.14 ; $P<0.0001$) and younger age ($B=-0.04$; 95%CI: -0.06 , -0.01 ; $P=0.015$). However, IOP ($P=0.29$) and AL ($P=0.49$) were no longer significantly correlated with ΔSE.

Predictor of Clinically Significant ΔSE The ROC curves (Figure 2) showed three models to predict clinically significant ΔSE (≥ 0.50 D). The models based on the multivariate linear regression analysis were as follows.

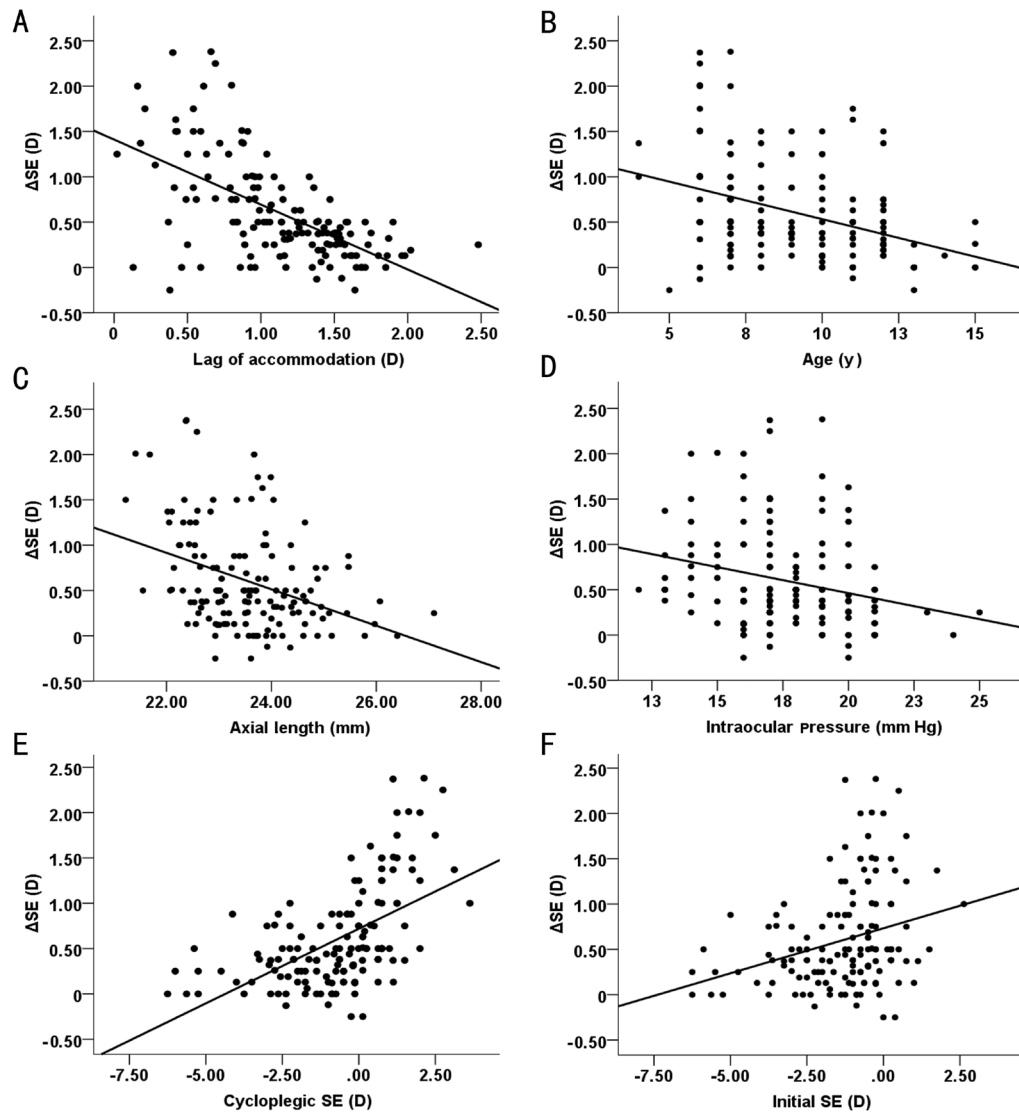


Figure 1 Relationship between Δ SE after cycloplegia and factors including lag of accommodation, age, axial length, intraocular pressure, cycloplegic SE, and initial SE ($n=145$) Δ SE: Change of spherical equivalent; D: Diopter.

Table 5 Multiple linear regression analysis of association between Δ SE and potential associated factors including cycloplegic SE $n=145$

Factor	β	<i>B</i>	95%CI	<i>t</i>	<i>P</i>	VIF
LOA	-0.45	-0.54	-0.69, -0.38	-7.00	<0.0001	1.16
Cycloplegic SE	0.33	0.10	0.06, 0.14	4.84	<0.0001	1.30
Age	-0.16	-0.04	-0.06, -0.01	-2.47	0.015	1.17
IOP	NA	NA	NA	-1.06	0.29	1.15
AL	NA	NA	NA	0.70	0.49	2.51

Δ SE: Change of spherical equivalent after cycloplegia with cyclopentolate; β : Standardized correlation coefficient; *B*: Regression coefficient; CI: Confidence interval; VIF: Variance inflation factor; LOA: Lag of accommodation; SE: Spherical equivalent; IOP: Intraocular pressure; AL: Axial length.

Model 1: Δ SE=-0.72×LOA+1.41

Model 2: Δ SE=0.66×LOA-0.15×AL+4.76

Model 3: Δ SE=-0.63×LOA-0.10×AL-0.04×age+4.12

According to the AUC, LOA predicted clinically significant Δ SE (≥ 0.50 D) by 82% (AUC=0.82) alone while the value was slightly improved to 85% (AUC=0.85) in combination

with AL and 86% (AUC=0.86) in association with AL as well as age. When LOA was taken into consideration alone, the best combination of sensitivity (80%) and specificity (79%) reached at 1.15 D of LOA. In detail, among those with the Δ SE of 0.50 D or more, there was an 80% probability that the LOA was 1.15 D or less (sensitivity). Meanwhile, among those with

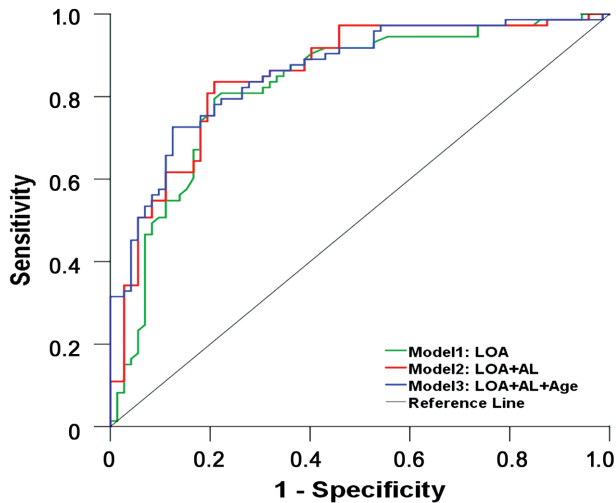


Figure 2 ROC curves showing three models to predict clinically significant Δ SE (≥ 0.50 D) induced by 1% cyclopentolate. Δ SE: Change of spherical equivalent; AUC: Area under curve; LOA: Lag of accommodation; AL: Axial length. D: Diopter; AUC for Model 1 (green line): 0.82; AUC for Model 2 (red line): 0.85; AUC for Model 3 (blue line): 0.86.

the Δ SE less than 0.50 D after cycloplegia with cyclopentolate, there was a 79% probability that the LOA was above 1.15 D (specificity).

DISCUSSION

In this study, it was proved for the first time that LOA played a greater role in predicting clinically significant Δ SE (≥ 0.50 D) than AL and age after application of cyclopentolate. The clinically significant Δ SE (≥ 0.50 D) was more likely to occur in children with LOA less than 1.15 D. This could provide a new clinical reference for the application of cyclopentolate to avoid unnecessary side effects and waiting time.

LOA is defined as a condition when the actual accommodative response level is lower than accommodative stimulus level. Due to the depth of focus, the accommodative response usually tends to be less than accommodative stimulus and thus most eyes tend to show accommodative lag. Besides, LOA was proved to be influenced by various factors, such as measuring method, accommodative stimulus, illumination, spatial frequency, age and refractive status^[12-15]. In current study, significant differences of LOA were found among different refractive groups ($P < 0.0001$) but not between gender groups ($P = 0.66$). The LOA measured in the myopia group (+1.28 D) was significantly larger than that in the hyperopia group (+0.88 D). For one thing, the subjects enrolled in our study had no history of refractive correction and more LOA often occurred in myopic eyes without correction for a long time. For another, the measurement of LOA was carried out under full correction, and myopic eyes needed to overcome additional accommodative stimulation caused by negative lens. Interestingly, LOA of emmetropic group (+1.12 D) was close

to that of the myopic group (+1.28 D, $P > 0.05$) in current study. The probable reason might be that the SE of 68% (26/38) emmetropic eyes were less than -0.50 D under noncycloplegic condition and then the accommodative status was similar between myopia and emmetropia groups.

It was proved for the first time that the change of SE after cycloplegia was smaller in eyes with larger LOA. However, the exact mechanism was not clear, which might be associated with the decrease of ciliary muscle contractility. Some *in vitro* experiments proved that the smooth muscle tissue cultured *in vitro* showed hypertrophy, stiffness and decreased contractility under mechanical stress^[16-18]. Other studies also reported that myopia was usually accompanied by ciliary hypertrophy^[19-21]. Bailey *et al*^[20] found that the ciliary body thickness 2 mm and 3 mm away from the scleral spur in 53 children aged 8 to 15y increased with the deepening of myopia as well as the growing of AL. They hold that the hypertrophy of ciliary muscle in high myopia eyes could lead to fibrosis and a large amount of collagen deposition, which consequently affected the contraction of ciliary muscle^[20]. Besides, the long-term stimulation of M receptor on ciliary muscle by low-level acetylcholine in myopic eyes might lead to the decrease of the number of receptors or the degradation of their function, which required further studies.

In contrast, Doherty *et al*^[9] reported no significant association of Δ SE with LOA ($P = 0.08$) by multiple analysis of variance in 128 British children aged 6 to 13y. There were three main reasons for the difference between Doherty's and this study's results: one was the measuring method of LOA; the second was the refractive distribution; the third was the data type of LOA. First, the measuring method of LOA in Doherty's study (Nott retinoscopy)^[9], compared to that adopted in current study (open-field automatic optometry), was more subject and more likely to underestimate LOA. Previous studies had found poor consistency between Nott retinoscopy and open-field automatic optometry^[12-13]. Manny *et al*^[12] compared three different methods to obtain LOA of 168 children aged 8 to 12y and found that LOA measured by MEM or Nott retinoscopy were generally lower than LOA measured by open field optometry, and that the difference increased significantly with LOA. Manny *et al*^[12] pointed out that both MEM and Nott retinoscopy lacked sufficient sensitivity (57% and 30%, respectively) to detect accommodative lag of 1.00 D or above. In current study, the range of LOA measured by open field refractometer was wide (0.02-2.48 D), and more than half of them (85/145) reached up to 1.00 D or more, which might be an important reason for different conclusions in our study from Doherty *et al*'s^[9]. Second, the number of hyperopic eyes was about twice that of emmetropic eyes and the proportion of myopia was very low (3/128) in Doherty *et al*'s study^[9],

however, more myopic eyes (67/145) were included in our study, with the proportion of hyperopia and emmetropia close to 1:1. Third, LOA was taken as a continuous variable in current study while it was transformed into a categorical variable which might cause certain information loss and weaken the potential correlation with Δ SE in Doherty *et al's*^[9] study.

Besides, children with more hyperopic cycloplegic SE (or shorter AL) and younger age were proved to have more hyperopic Δ SE after cycloplegia, which was in agreement with previous studies^[9-11,22]. This could partly result from larger amplitude of accommodation and easier intervention of accommodation during examinations for more hyperopic and younger children. Furthermore, compared with cycloplegic SE, AL was excluded from the regression model (Table 5). The partial correlation analysis showed that cycloplegic SE was still significantly positively correlated with Δ SE ($r=0.44$, $P<0.05$) with AL controlled, indicating that other non-axial factors (*e.g.* lens thickness and curvature) might be associated with the Δ SE after cycloplegia. However, as a parameter measured after cycloplegia, cycloplegic SE was not suitable to be an indicator of Δ SE after cycloplegia. Therefore, we only analyzed the regression model not including cycloplegic SE in current study.

No significant association was observed between IOP and Δ SE in multivariate analysis in either model (Tables 4 and 5) in current study. IOP was reported to be correlated with Δ SE in a few studies^[5,11], however, it was only demonstrated in bivariate correlation analysis (Spearman's $r=-0.29$, $P=0.0001$) in our study. This suggested that IOP played a weaker role than other factors eventually enrolled. Initial SE was not significantly correlated with Δ SE in multivariate analysis (Table 4), mainly because that noncycloplegic SE was easily susceptible to the effects of accommodation and couldn't reflect the real refractive status.

The limitations of current study were as follows. First, the models constructed in this study were applied to judging whether the Δ SE would be clinically significant (over 0.50 D) but they were not accurate enough to predict Δ SE directly. Further studies are required to establish more accurate models which may need to include more factors associated with the accommodation. Second, all the children in current study showed LOA. More studies are under way to make sure whether the conclusion will still be applicable in those whose accommodative response exceeds accommodative stimulus.

In conclusion, the Δ SE of children with less LOA, more hyperopic refractive error and younger age tend to be larger after cycloplegia with cyclopentolate. Especially, LOA plays a decisive role and is able to predict clinically significant Δ SE (at least 0.50 D) alone. For children who have large LOA,

cyclopentolate hydrochloride is not the first choice to induce cycloplegia. Therefore, this study provides a new reference for clinicians to reasonably use cyclopentolate hydrochloride eye drops, so as to reduce the side effects of drugs, shorten the waiting time as well as improve the medical experience of patients.

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