• Clinical Research •

Low-concentration atropine (0.01%) on quantitative contrast sensitivity function in Chinese children with myopia

Yu-Hao Ye[1,2,3,4], *Yi-Yong Xian*[1,2,3,4], *Fang Liu*[1,2,3,4], *Zhong-Lin Lyu*[5,6,7], *Xing-Tao Zhou*[1,2,3,4], *Jing Zhao*[1,2,3,4]

[1]Department of Ophthalmology and Optometry, Eye & ENT Hospital of Fudan University, Shanghai 200031, China
[2]NHC Key Laboratory of Myopia (Fudan University), Key Laboratory of Myopia, Chinese Academy of Medical Sciences, Shanghai 200000, China
[3]Shanghai Research Center of Ophthalmology and Optometry, Shanghai 200000, China
[4]Shanghai Engineering Research Center of Laser and Autostereoscopic 3D for Vision Care (20DZ2255000). Shanghai 200030, China
[5]Division of Arts and Sciences, NYU Shanghai, Shanghai 200000, China
[6]Center for Neural Science and Department of Psychology, New York University, New York 10012, USA
[7]NYU-ECNU Institute of Brain and Cognitive Science, NYU Shanghai, Shanghai 200000, China
Co-first authors: Yu-Hao Ye and Yi-Yong Xian
Correspondence to: Jing Zhao and Xing-Tao Zhou. Department of Ophthalmology, Eye & ENT Hospital of Fudan University; NHC Key Laboratory of Myopia; Laboratory of Myopia, Chinese Academy of Medical Sciences, 83 Fenyang Road, Shanghai 200031, China. zhaojing_med@163.com; doctzhouxingtao@163.com
Received: 2024-07-28 Accepted: 2024-11-12

Abstract

• **AIM:** To investigate the effect of 0.01% low-concentration atropine (LA) on quantitative contrast sensitivity function (qCSF) in children with myopia.

• **METHODS:** This paired case-control study included 90 eyes of 58 children who were sex-, age-, and refraction-matched and equally divided into two groups: the 0.01% LA group had undergone 6mo use of daily 0.01% atropine and control group was naïve to LA. Routine ophthalmic examinations and qCSF test without refractive correction were performed. Two groups were compared in monocular and binocular qCSF parameters, including the area under logCSF, CSF acuity, and contrast sensitivity (CS) at 1.0-18.0 cycle per degree (cpd).

• **RESULTS:** In the monocular comparison, the CSF acuity of the LA group was significantly higher than that of the control group (7.58±5.51 *vs* 6.37±4.22 cpd, $P<0.05$). The subgroup analysis showed that in the 6-9y group, CSF acuity was significantly higher in the LA group than the control group (8.76±6.19 *vs* 6.54±4.25 cpd, $P<0.05$), and in the Female group, low refraction sphere group, and high refraction cylinder group, the CS at high spatial frequencies (12.0 and 18.0 cpd) were significantly higher in the LA group than in the control group (all $P<0.05$). In the binocular test, CSF acuity and CS at 12.0 cpd were significantly higher in the LA group than in the control group (10.95±7.00 *vs* 8.65±5.12 cpd; 0.17±0.33 *vs* 0.06±0.16, respectively; both $P<0.05$).

• **CONCLUSION:** Use of LA may result in improved CS in children with early onset myopia.

• **KEYWORDS:** low-concentration atropine; myopia; quantitative contrast sensitivity function; Chinese children
DOI:10.18240/ijo.2025.01.14

Citation: Ye YH, Xian YY, Liu F, Lyu ZL, Zhou XT, Zhao J. Low-concentration atropine (0.01%) on quantitative contrast sensitivity function in Chinese children with myopia. *Int J Ophthalmol* 2025;18(1):117-124

INTRODUCTION

Myopia has become a global public health concern. In China, the prevalence is approximately 30.7% among children aged 7-12y[1]. It is estimated that half of the world's population may suffer from myopia by 2050, with high myopia reaching 10%[2]. It is of great importance and necessity to reduce the reliance on corrective methods and reduce global visual impairments with active prevention and management of myopia[3]. Low-concentration atropine (LA) has been reported to slow the progression of myopia, apart from outdoor activities and optical interventions, such as orthokeratology[4-7]. Studies have found that atropine may increase the release of retinal dopamine[8], inhibit scleral remodeling[9-10], and promote

the thickening of the choroid to prevent axial elongation[11-12]. In a Meta-analysis, 0.01% LA was reported to reduce axial elongation by 0.15 mm/y[13]. A higher concentration may provide better outcomes, but the rebound effect and incidence of side effects, including anaphylaxis, poor near vision, and allergy, would increase in a dose-dependent manner[14]. Contrast sensitivity (CS) is a vital feature of visual function that is influenced by optical conditions and neural processing in the visual pathway[15]. CS refers to the contrast ratio required to distinguish an object from its background[16], and it is usually represented as a CS function (CSF) to express the relationship between contrast thresholds and spatial frequencies, which reflects the ability of human eyes to detect objects in daily life. Studies regarding the effect of LA on CS are still lacking, and in particular CS has not been fully evaluated in children using LA[17-18]. Lesmes *et al*[19] developed the quantitative CSF (qCSF) test with the Bayesian adaptive algorithm, which accurately and efficiently estimates the curve of the CSF[20]. The qCSF test has been applied to assess eye diseases including glaucoma[21], amblyopia[22], and diabetic retinopathy[23]. Given the potentially wide biological effects of atropine in the eye, its long-term safety deserves more attention, especially in the retina and visual pathways. Several studies have shown that LA has no significant effect on corrected distance visual acuity (CDVA)[4-5,24], while studies using electroretinography found a potential effect of atropine on retinal neural activity[25-26], especially on the inner layers of the peripheral retina to affect neuronal responses to myopic defocus[26]. The LA affected CS in children with myopia might be the intermedium between these two processes. In addition, a better understanding of the effects of LA on children with different characteristics will help with further investigation of its potential mechanisms and provide a basis for screening possible LA-applicable populations. Therefore, this study compared the results of the qCSF test in myopic children using 0.01% LA and control children and assessed the potential impact of 0.01% LA eye drops on CSF.

PARTICIPANTS AND METHODS

Ethics Approval This case-control study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Eye and ENT Hospital of Fudan University (ID:2020107). After explaining the risks and benefits of the study, all the participants and their legal guardians provided informed consent.

Children aged 6-14y who were admitted to the Eye and ENT Hospital of Fudan University from December 2021 to January 2022 were enrolled. Children who had been using 0.01% LA eye drops every night for 6mo were included in the LA group. For the control group, demographically matched children who were naïve to LA were selected. The matching criteria were: 1) same sex; 2) age differences ≤1y; 3) differences in spherical equivalent (SE)≤0.25 D (differences in SE of both eyes ≤0.25 D in the binocular analysis).

The exclusion criteria were as follows: 1) history of contact lens use; 2) history of strabismus, amblyopia, or congenital cataract; 3) history of ocular trauma or surgery; 4) history of systemic diseases; 5) history of mental or psychological illness.

Examinations 1) Cycloplegic optometry: tropicamide phenylephrine eye drops (Mydrin-P, Santen, Osaka, Japan) was applied once every 5min for 5 cycles for cycloplegia. Thirty minutes after the last application and when the light reflex disappeared, the RT-5100 Refractor (Nidek Technologies, Japan) was used to examine the refraction sphere (RS), refraction cylinder (RC), cylindrical axis, and CDVA. 2) The Humphery IOL Master700 (Carl Zeiss Meditec Ltd, Jena, Germany) was used to measure the axial length (AL) and corneal keratometry, including mean keratometry (Km), keratometry of the flattest meridian and the steepest meridian.

Quantitative Contrast Sensitivity Function Test The qCSF test was carried out at least 30min after cycloplegia without refractive correction. An NEC P403 monitor (Gension & Waltai Digital Video System Co. Ltd. China) was adopted, with the display area of 116.84 cm×77.89 cm, resolution of 1920×1080 pixels, brightness of 550 cd/m^2, and contrast ratio of 4000:1. The visual stimuli consisted of 10 digits in Sloan fonts, with 128 contrast levels and 19 spatial frequencies[27-28]. The participants observed the stimuli horizontally at 3 m in a mesopic environment. For each round of testing, three digits with the same spatial frequency and decreasing contrast ratio were presented on the screen, and the technician would input the results into the control tablet according to the subject's response. The computer program automatically provided the next round of visual stimuli until 25 rounds were completed. First, the test was performed unilaterally with the other eye covered, and then, the binocular test was conducted. A 1-minute rest between each set of tests was given to reduce eye strain. The results of the qCSF test were recorded for analysis, including the area under log contrast sensitivity function (AULCSF), cutoff spatial frequency (CSF acuity), and CS (log units) at 1.0, 1.5, 3.0, 6.0, 12.0, and 18.0 cycles per degree (cpd).

Statistical Analysis Continuous variables were presented as mean±standard deviation (SD), while categorical variables were expressed as frequencies. In the subgroup analysis, subjects were classified according to age (6-9y and 10-13y), sex (female and male), RS (high RS group: RS≤-1.0 D; low RS group: RS>-1.0 D), RC (high RC group: RC≤-0.5 D; low RC group: RC>-0.5 D), and SE (high SE group: SE≤-1.0 D; low SE group: SE>-1.0 D). The Kolmogorov-Smirnov test was used as a normality test. The paired *t*-test and paired Wilcoxon

signed-rank test were used to examine inter-group differences between normal and non-normal paired samples, respectively. The generalized estimating equation was used to compare the inter-group differences in paired samples while controlling confounding factors (inter-eye correlation, axial length, CDVA, and keratometry, aside from matching factors). Analysis of variance was used to compare differences among the three groups (the classified age, sex and refractive error groups). The Statistical Package for the Social Sciences (version 25.0, SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. All data were tested two-sided, and $P<0.05$ was considered statistically significant.

RESULTS

A total of 90 eyes of 58 subjects were enrolled. The LA group included 45 eyes of 26 patients (male/female: 13/13) while the control group included 45 eyes of 32 patients (male/female: 18/14). All subjects successfully completed the qCSF tests without refractive correction, and the loss rate for all types of data was less than 5%. The demographic data were shown in Table 1.

Table 1 Patient demographics mean±SD

Characteristics	LA group	Control group	*P*
Age (y)	9.16±1.87	9.46±2.06	0.261
Gender (male/female)	13/13	18/14	-
Axial length (mm)	24.05±0.77	24.15±0.87	0.494
RS (D)	-1.18±0.94	-1.03±0.96	0.019
RC (D)	-0.46±0.54	-0.72±0.74	0.030
SE (D)	-1.41±0.96	-1.39±0.94	0.368
K1 (D)	42.79±1.26	42.85±1.60	0.883
K2 (D)	44.02±1.48	44.26±1.46	0.552
Km (D)	43.41±1.36	43.56±1.48	0.707
CDVA (logMAR)	0±0.02	0±0.01	0.015

LA: Low-concentration atropine; RS: Refraction sphere; RC: Refraction cylinder; SE: Spherical equivalent; K1: Keratometry of the flattest meridian; K2: Keratometry of the steepest meridian; Km: Mean keratometry; CDVA: Corrected distance visual acuity.

qCSF Characteristics Between Groups The mean values and inter-group differences in the qCSF parameters in the LA and control groups are shown in Table 2 and Figure 1. Pair *t*-tests showed no significant differences between the two groups ($P>0.05$).

Pearson's correlation analysis showed that CSF acuity was significantly and positively correlated with age and RS ($r=0.332$, $P=0.026$; $r=0.311$, $P=0.037$) and negatively correlated with RC ($r=-0.308$, $P=0.040$). AL was positively correlated with CS at low spatial frequencies (1.0 and 1.5 cpd) ($r=0.437$, $P=0.005$; $r=0.389$, $P=0.014$) and negatively correlated with CS at high spatial frequencies (12.0 and 18.0 cpd; $r=-0.376$, $P=0.018$; $r=-0.353$, $P=0.017$). The CS at low and medium spatial frequencies (1.0, 1.5, and 3.0 cpd) were negatively correlated with Km ($r=-0.553$, $P=0.001$; $r=-0.518$, $P=0.001$; $r=-0.368$, $P=0.030$). The CS at high spatial frequencies (12.0 and 18.0 cpd) were negatively correlated with logMAR CDVA ($r=-0.370$, $P=0.012$; $r=0.417$, $P=0.004$).

Generalized estimating equation (GEE) analysis showed that CSF acuity in the LA group was significantly higher than that in the control group (7.58±5.51 *vs* 6.37±4.22 cpd, $P=0.039$), while other parameters were not significantly different ($P>0.05$).

Subgroup Analysis Table 3, Figures 2 and 3 show the subgroup comparison of qCSF parameters according to age, sex, and refractive error. In the 6-9y group, the CSF acuity in LA group was significantly higher compared to control group (8.76±6.19 *vs* 6.54±4.25 cpd, $P=0.020$). The CS at high spatial frequencies (12.0 and 18.0 cpd) in the 6-9 years group (all $P<0.001$), female group ($P=0.001$ at 12.0 cpd and $P<0.001$ at 18.0 cpd), low RS group (all $P<0.001$), high RC group ($P=0.035$ at 12.0 cpd and $P<0.001$ at 18.0 cpd), and low SE group (all $P<0.001$) were significantly higher in the LA group compared to control group.

Comparison of Binocular Quantitative Contrast Sensitivity Function Parameters Figure 4 show the differences in binocular qCSF parameters between the two groups. The GEE analysis showed that binocular CSF acuity and CS at 12.0 cpd were significantly higher in the LA group than that in the control group (10.95±7.00 *vs* 8.65±5.12 cpd for CSF acuity, $P=0.031$; 0.17±0.33 *vs* 0.06±0.16 for CS at 12.0 cpd, $P=0.025$).

DISCUSSION

LA eye drop is a commonly used and effective method for myopia control[13], which exerts extensive biological effects on the eye[29]. Therefore, the safety of the long-term use of LA in children requires evaluations from different perspectives. CS demonstrates the ability to distinguish objects of different sizes and is affected jointly by the optical properties and neural processing of the visual pathway. The qCSF test can be applied to the evaluation of visual function as an important feature[15]. The qCSF test developed in recent years provides a fast and comprehensive assessment of CS, which is applicable in pediatric patients[20]. This study firstly investigated the effect of 0.01% LA on qCSF parameters without refractive correction in children with myopia, which provides reference values for the safety of applying LA in children.

No significant difference was found between the two groups in the paired *t*-test, which was inconsistent with the results of the GEE analysis (Table 2). A possible reason may be that only age, sex, and SE were matched between the two groups; however, correlation analysis showed that qCSF parameters were significantly correlated with AL, corneal keratometry, and CDVA, which may affect the results of paired tests, in addition to the inter-eye correlation. GEE analysis included all these confounding factors and showed a significant difference

Table 2 qCSF results in LA and control groups mean±SD

Characteristic	LA group	NC group	Δ (LA-NC)	*P* (paired *t*)	*P* (GEE)
AULCSF	0.35±0.28	0.32±0.26	0.03±0.27	0.450	0.250
CSF acuity	7.58±5.51	6.37±4.22	1.21±5.49	0.146	0.039
CS (1.0 cpd)	0.92±0.26	0.88±0.33	0.04±0.31	0.356	0.476
CS (1.5 cpd)	0.82±0.29	0.77±0.37	0.05±0.36	0.330	0.406
CS (3.0 cpd)	0.49±0.38	0.49±0.4	0±0.40	0.949	0.626
CS (6.0 cpd)	0.23±0.31	0.19±0.28	0.04±0.28	0.406	0.213
CS (12.0 cpd)	0.05±0.17	0.02±0.06	0.03±0.19	0.237	0.149
CS (18.0 cpd)	0.02±0.07	0±0	0.02±0.07	0.126	0.072

qCSF: Quantitative contrast sensitivity function; LA: Low-concentration atropine; AULCSF: Area under logCSF; CS: Contrast sensitivity; GEE: Generalized estimating equation.

Table 3 Comparison of qCSF results between LA group and control group in differently stratified groups

Parameters	Age (y)		Gender		RS		RC		SE	
	6-9	10-13	Female	Male	≤-1.0 D	>-1.0 D	≤-0.5 D	>-0.5 D	≤-1.0 D	>-1.0 D
AULCSF										
LA	0.42±0.30[b]	0.23±0.19[b]	0.35±0.30	0.36±0.26	0.20±0.20[b]	0.51±0.26[b]	0.39±0.39	0.34±0.23	0.20±0.19[b]	0.56±0.24[b]
Control	0.35±0.28	0.29±0.21	0.27±0.23	0.37±0.27	0.15±0.17	0.47±0.22	0.37±0.28	0.29±0.23	0.16±0.15[b]	0.55±0.18[b]
CSF acuity										
LA	8.76±6.19[a]	5.43±3.15	7.38±6.14	7.75±5.01	4.70±3.01	10.58±5.96	8.93±7.97[b]	7.14±4.51[b]	4.62±2.85[b]	11.62±5.75[b]
Control	6.54±4.25[a]	6.09±4.28	5.30±2.95	7.30±4.95	3.96±3.23	8.48±3.87	7.40±4.96	5.54±3.39	3.98±2.93[b]	9.63±3.47[b]
CS (1.0 cpd)										
LA	0.98±0.25[b]	0.82±0.26[b]	0.99±0.20[b]	0.86±0.30[b]	0.78±0.26[b]	1.07±0.17[b]	0.81±0.26	0.96±0.26	0.80±0.25[b]	1.09±0.17[b]
Control	0.87±0.36[b]	0.89±0.28[b]	0.86±0.29	0.90±0.36	0.68±0.35[b]	1.05±0.17[b]	0.88±0.31	0.88±0.34	0.73±0.35[b]	1.08±0.13[b]
CS (1.5 cpd)										
LA	0.89±0.28[b]	0.70±0.27[b]	0.87±0.22	0.78±0.34	0.65±0.28[b]	1.00±0.17[b]	0.75±0.30	0.85±0.29	0.67±0.27[b]	1.03±0.15[b]
Control	0.78±0.39	0.75±0.33	0.71±0.37	0.82±0.36	0.52±0.36[b]	0.99±0.20[b]	0.78±0.37	0.76±0.37	0.56±0.34[b]	1.05±0.13[b]
CS (3.0 cpd)										
LA	0.58±0.39[b]	0.33±0.32[b]	0.46±0.37	0.53±0.40	0.27±0.33[b]	0.73±0.29[b]	0.49±0.44	0.50±0.37	0.27±0.31[b]	0.81±0.22[b]
Control	0.52±0.43	0.44±0.35	0.44±0.40	0.53±0.41	0.21±0.28[b]	0.73±0.33[b]	0.55±0.44	0.45±0.37	0.22±0.26[b]	0.86±0.23[b]
CS (6.0 cpd)										
LA	0.29±0.34	0.10±0.19	0.20±0.35	0.24±0.27	0.08±0.21[b]	0.38±0.33[b]	0.30±0.44	0.20±0.25	0.07±0.19[b]	0.44±0.31[b]
Control	0.24±0.30	0.12±0.22	0.14±0.22	0.24±0.31	0.04±0.13[b]	0.33±0.30[b]	0.26±0.30	0.13±0.25	0.03±0.12[b]	0.41±0.28[b]
CS (12.0 cpd)										
LA	0.08±0.21[a]	0±0.01	0.08±0.23[a]	0.03±0.09	0±0.01[b]	0.10±0.24[a,b]	0.15±0.31[a]	0.02±0.08	0±0.01[b]	0.12±0.25[a,b]
Control	0.02±0.06[a]	0.02±0.06	0±0[a]	0.04±0.07	0.01±0.04	0.03±0.07[a]	0.03±0.07[a]	0.01±0.05	0.01±0.03	0.04±0.08[a]
CS (18.0 cpd)										
LA	0.03±0.09[a]	0±0	0.03±0.10[a]	0±0.01	0±0[b]	0.03±0.10[a,b]	0.06±0.14[a]	0±0.01	0±0[b]	0.04±0.11[a,b]
Control	0±0[a]	0±0	0±0[a]	0±0	0±0	0±0[a]	0±0[a]	0±0	0±0	0±0[a]

CSF: Contrast sensitivity function; qCSF: Quantitative contrast sensitivity function; AULCSF: Area under logCSF; CS: Contrast sensitivity; RS: Refraction sphere; RC: Refraction cylinder; SE: Spherical equivalent; LA: Low-concentration atropine. [a]*P*<0.05, LA group *vs* control group; [b]*P*<0.05 between differently stratified groups in LA group or control group.

of higher CSF acuity in the LA group compared with the control group (Table 2). In subgroup analysis, the CS at high spatial frequencies (12.0 and 18.0 cpd) in the 6-9y group were significantly lower in control group (Table 3), indicating that LA may affect the CS at high spatial frequency, and that this effect was more prominent in younger children without refractive correction. Atropine has a wide range of biological effects in the eye, including inhibition of pupil contraction, promotion of the release of retinal dopamine, and increasing choroidal blood flow[29], which further causes an increase in subfoveal choroidal thickness and shortening of the AL[30-31]. Shortening of AL may reduce the level of defocus in myopic children, which may result in a higher CSF acuity in the LA group than in the control group.

Studies indicate that nightly administration of 0.01% LA for 4wk had no significant impact on the best-corrected visual

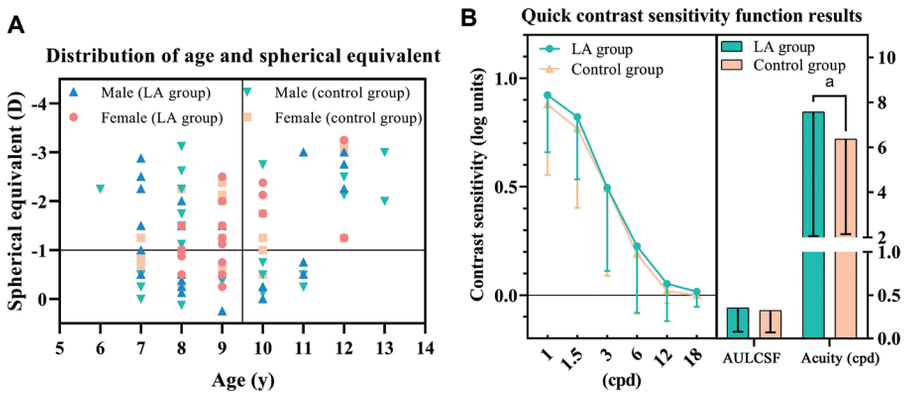

Figure 1 Patient distributions and average qCSF results of 0.01% LA and control groups A: Distribution of age and spherical equivalents in subjects; B: Average qCSF values. Left: Contrast sensitivity (log units) at different spatial frequencies (cpd). Right: Average AULCSF and CSF acuity (cpd). [a]*P*<0.05. CSF: Contrast sensitivity function; qCSF: Quantitative CSF; LA: Low-concentration atropine; AULCSF: Area under logCSF; cpd: Cycle per degree.

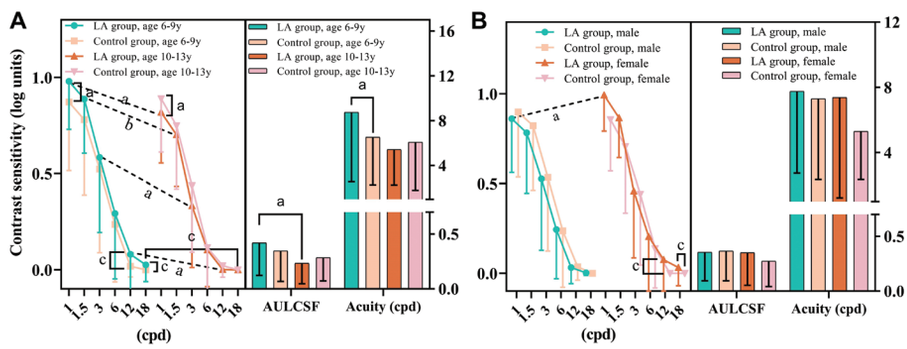

Figure 2 Group analyses of qCSF parameters according to age and sex A: qCSF parameters in the 6-9y and 10-13y groups; B: qCSF parameters in the male and female groups. [a]*P*<0.05; [b]*P*<0.01; [c]*P*<0.001. qCSF: Quantitative contrast sensitivity function; AULCSF: Area under log contrast sensitivity function; cpd: Cycle per degree.

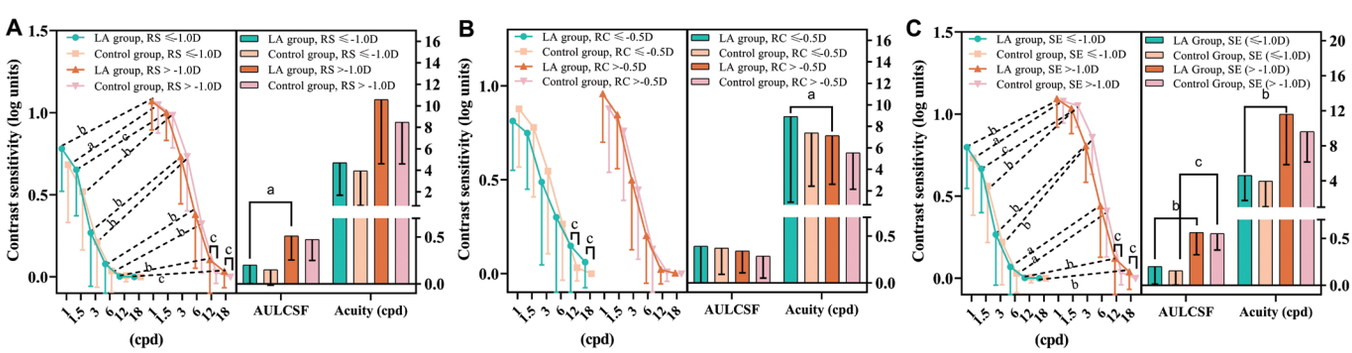

Figure 3 Group analyses of qCSF parameters according to refractive errors A: qCSF parameters in the low RS group (RS>-1.0 D) and high RS group (RS≤-1.0 D); B: qCSF parameters in the low RC group (RC>-0.5D) and the high RC group (RC≤-0.5 D); C: qCSF parameters in the low SE group (SE>-1.0 D) and high SE group (SE≤-1.0 D). [a]*P*<0.05; [b]*P*<0.01; [c]*P*<0.001. qCSF: Quantitative contrast sensitivity function; RS: Refraction sphere; RC: Refraction cylinder; SE: Spherical equivalent.

acuity (BCVA) in myopic adults[17]. Yam *et al*[5] demonstrated that the use of 0.05%, 0.025%, and 0.01% LA for 2y did not significantly influence distance or near BCVA in children. On the one hand, our findings suggested that LA did not have a significantly negative impact on children's CSF function without refractive correction, which was consistent with the above findings. On the other hand, this study showed that LA may improve CS in children, which was different from previous studies. A possible reason may be that CS was assessed without refractive correction, and the duration of LA administration was 6mo in the present study. Previous studies have revealed that atropine could improve CS in mice and chickens for a short period of time, which was presumably related to the increase in brightness of retinal images resulting from pupil dilation or the increased release of retinal dopamine[32-33]. Therefore, it is speculated that long-term LA use may enhance this process and thereby improve CSF acuity in children. In the present study, the CS in children

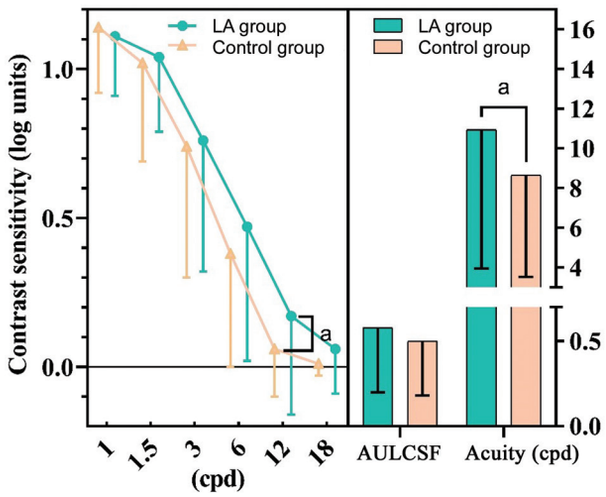

Figure 4 Binocular qCSF parameters in the 0.01% LA group and control groups CS at 12.0 cpd and CSF acuity were significantly different between the LA and control groups. [a]*P*<0.05. qCSF: Quantitative contrast sensitivity function; LA: Low-concentration atropine; AULCSF: Area under log contrast sensitivity function; cpd: Cycle per degree.

was examined without refractive correction. Compared with the visual acuity test, the qCSF test can reflect the contrast threshold at various spatial frequencies and represent the visual function and its changes in children more comprehensively and sensitively[16]. As a result, this study suggested that LA did not have a significantly negative effect on children's CSF but may improve it instead.

The female group was similar to the 6-9y group, in which CS at high spatial frequencies (12.0 and 18.0 cpd) were higher in the LA group than control group (Table 3). Younger age and female sex were suggested to be risk factors for the natural progression of myopia[34], while our study found similar changes in CS in the two subgroups. Although atropine mediates choroidal thickness to control axial growth[35], the resulting changes in choroidal thickness were not significantly correlated with sex, but mainly with the concentration of atropine[34-35]. Therefore, atropine may improve CS in children through other mechanisms, and the different endocrine and developmental characteristics between boys and girls[36] may lead to differences in the effects of atropine. Changes in choroidal thickness were not evaluated in this study, and it would be difficult to determine the reasons for the differences in CS changes in different age and sex groups and their correlation with myopia control. Therefore, this study demonstrates that for myopic children of different ages and sexes, there may be differences in the effects of LA on CS without refractive correction, while the specific effects and reasons still need to be clarified by further research.

In groups with RS or SE within -1.0 D, CS at high spatial frequencies was improved in the LA group (Table 3), while in clinical practice, -1.0 D of sphere is usually defined as an indication to prescribe spectacles for children. Our findings indicate that 0.01% LA may improve visual performance at high spatial frequencies in children with low myopia, which may be explained by the subfoveal choroidal thickening and decreased central myopic defocus induced by LA[30-31]. At medium and low spatial frequencies, LA use did not cause such changes, which was speculated to be less sensitive to changes in myopic defocus[37]. In children with myopia over -1.0 DS, LA had no significant effect on qCSF parameters, probably because the reduction in myopic defocus caused by LA was small relative to the children's refractive error, and thus the influence was not apparent. In the high RC group, CS at high spatial frequencies was higher in the LA group than in the control group (Table 3). Given that the influence of pupil dilation by atropine[34] was minimized by full cycloplegia before the qCSF test and LA did not have a significant impact on corneal or crystalline curvature, the specific effect induced by LA and the reason for changes in CS among children with different astigmatism needs further investigation. Taken together, LA may improve CS at high spatial frequencies in children with mild myopia and may help improve visual performance without refractive correction.

In both monocular and binocular comparison, the CSF acuity and CS at 12.0 cpd were higher in the LA group than in the control group. Treatment with 0.01% LA was reported to have no significant impact on the vergence or accommodative convergence to accommodation ratio[38-39]. Our findings confirmed that LA did not impair binocular CSF in myopic children, and the increased CSF acuity and CS at high spatial frequencies may be associated with choroidal thickening induced by atropine[35,40].

This study has several limitations. First, the sample size was relatively small, and future prospective studies with large sample sizes are warranted to confirm the effect of LA on CS in children. Second, atropine eye drops with higher concentrations (0.025%, 0.05%, and 0.1%) have attracted much attention in recent years[5]. Further research on different concentrations of atropine will help reveal the dose-dependent effects of atropine on qCSF parameters in children.

In conclusion, this study revealed the effect of 0.01% LA for 6mo on qCSF parameters in myopic children without refractive correction, in which 0.01% LA may improve CSF acuity. The CS at high spatial frequencies was higher in the LA group among children with young age, female sex, low myopia and high astigmatism. These findings suggest the use of LA may result in improved CS in children with early onset myopia.

ACKNOWLEDGEMENTS

Authors' contributions: Study concept and design (Ye YH, Xian YY, Zhao J, Zhou XT); data collection (Xian YY, Ye YH,

Liu Fang, Zhao J); data analysis and interpretation (Ye YH, Xian YY); drafting of the manuscript (Xian YY, Ye YH, Zhao J); critical revision of the manuscript (Xian YY, Ye YH, Lyu ZL, Zhao J, Zhou XT); supervision (Zhou XT, Zhao J). All authors read and approved the final manuscript.

Foundation: Supported by National Key Research and Development Program of China (No.2023YFA0915000)

Conflicts of Interest: Ye YH, None; **Xian YY,** None; **Liu F,** None; **Lyu ZL** holds intellectual property interests in visual function measurement and rehabilitation technologies and equity interests in Adaptive Sensory Technology, Inc. (San Diego, CA) and Juehua Medical Technology, Ltd (Beijing, China); **Zhou XT,** None; **Zhao J,** None.

REFERENCES

1 Dong L, Kang YK, Li Y, Wei WB, Jonas JB. Prevalence and time trends of myopia in children and adolescents in China: a Systemic Review and Meta-Analysis. *Retina* 2020;40(3):399-411.

2 Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, Wong TY, Naduvilath TJ, Resnikoff S. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016;123(5):1036-1042.

3 Bullimore MA, Brennan NA. Myopia control: why each diopter matters. *Optom Vis Sci* 2019;96(6):463-465.

4 Yam JC, Jiang YN, Tang SM, *et al*. Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. *Ophthalmology* 2019;126(1):113-124.

5 Yam JC, Li FF, Zhang XJ, Tang SM, Yip BHK, Kam KW, Ko ST, Young AL, Tham CC, Chen LJ, Pang CP. Two-year clinical trial of the low-concentration atropine for myopia progression (LAMP) study: phase 2 report. *Ophthalmology* 2020;127(7):910-919.

6 Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (ATROPINE FOR THE TREATMENT OF MYopia 2). *Ophthalmology* 2012;119(2):347-354.

7 Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL, Tan D. Atropine for the treatment of childhood myopia. *Ophthalmology* 2006;113(12):2285-2291.

8 Mathis U, Feldkaemper M, Wang M, Schaeffel F. Studies on retinal mechanisms possibly related to myopia inhibition by atropine in the chicken. *Graefes Arch Clin Exp Ophthalmol* 2020;258(2):319-333.

9 Barathi VA, Weon SR, Beuerman RW. Expression of muscarinic receptors in human and mouse sclera and their role in the regulation of scleral fibroblasts proliferation. *Mol Vis* 2009;15:1277-1293.

10 Barathi VA, Beuerman RW. Molecular mechanisms of muscarinic receptors in mouse scleral fibroblasts: Prior to and after induction of experimental myopia with atropine treatment. *Mol Vis* 2011;17:680-692.

11 Zhang ZW, Zhou YT, Xie ZF, Chen TT, Gu Y, Lu S, Wu ZF. The effect of topical atropine on the choroidal thickness of healthy children. *Sci Rep* 2016;6:34936.

12 Nickla DL, Zhu XY, Wallman J. Effects of muscarinic agents on chick choroids in intact eyes and eyecups: evidence for a muscarinic mechanism in choroidal thinning. *Ophthalmic Physiol Opt* 2013;33(3):245-256.

13 Huang JH, Wen DZ, Wang QM, *et al*. Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis. *Ophthalmology* 2016;123(4):697-708.

14 Gong QW, Janowski M, Luo M, Wei H, Chen BJ, Yang GY, Liu LQ. Efficacy and adverse effects of atropine in childhood myopia: a meta-analysis. *JAMA Ophthalmol* 2017;135(6):624-630.

15 Laycock R, Crewther SG, Crewther DP. A role for the 'magnocellular advantage' in visual impairments in neurodevelopmental and psychiatric disorders. *Neurosci Biobehav Rev* 2007;31(3):363-376.

16 Richman J, Spaeth GL, Wirostko B. Contrast sensitivity basics and a critique of currently available tests. *J Cataract Refract Surg* 2013;39(7):1100-1106.

17 Cheng ZY, Mei JH, Cao SQ, Zhang R, Zhou JW, Wang YW. The effects of 0.01% atropine on adult myopes' contrast sensitivity. *Front Neurosci* 2021;15:624472.

18 Kay CD, Morrison JD. The effects of a single intramuscular injection of atropine sulphate on visual performance in man. *Hum Toxicol* 1987;6(2):165-172.

19 Lesmes LA, Lu ZL, Baek J, Albright TD. Bayesian adaptive estimation of the contrast sensitivity function: the quick CSF method. *J Vis* 2010;10(3):17.1-1721.

20 Hou F, Huang CB, Lesmes L, Feng LX, Tao LM, Zhou YF, Lu ZL. qCSF in clinical application: efficient characterization and classification of contrast sensitivity functions in amblyopia. *Invest Ophthalmol Vis Sci* 2010;51(10):5365-5377.

21 João CAR, Scanferla L, Jansonius NM. Binocular interactions in glaucoma patients with nonoverlapping visual field defects: contrast summation, rivalry, and phase combination. *Invest Ophthalmol Vis Sci* 2021;62(12):9.

22 Jia Y, Ye QQ, Zhang SL, *et al*. Contrast sensitivity and stereoacuity in successfully treated refractive amblyopia. *Invest Ophthalmol Vis Sci* 2022;63(1):6.

23 Aiello L, Rhee J, Lesmes LA, Bittner AK, Sun JK. Bayesian adaptive contrast sensitivity function as a sensitive indicator of diabetic macular edema. *Invest Ophthalmol Vis Sci* 2017;58:935.

24 Loughman J, Flitcroft DI. The acceptability and visual impact of 0.01% atropine in a Caucasian population. *Br J Ophthalmol* 2016;100(11):1525-1529.

25 Khanal S, Rathod SN, Phillips JR. The acute effect of atropine eye drops on the human full-field electroretinogram. *Doc Ophthalmol* 2021;142(3):315-328.

26 Khanal S, Turnbull PRK, Lee N, Phillips JR. The effect of atropine on human global flash mfERG responses to retinal defocus. *Invest Ophthalmol Vis Sci* 2019;60(1):218-225.

27 Zheng HY, Shen ML, He XH, Cui R, Lesmes LA, Lu ZL, Hou F. Comparing spatial contrast sensitivity functions measured with digit and grating stimuli. *Transl Vis Sci Technol* 2019;8(6):16.

28 Zheng HY, Wang CX, Cui R, He XH, Shen ML, Lesmes LA, Lu ZL, Qu J, Hou F. Measuring the contrast sensitivity function using the qCSF method with 10 digits. *Transl Vis Sci Technol* 2018;7(6):9.

29 Upadhyay A, Beuerman RW. Biological mechanisms of atropine control of myopia. *Eye Contact Lens* 2020;46(3):129-135.

30 Jiang YJ, Zhang ZW, Wu ZF, Sun S, Fu YT, Ke BL. Change and recovery of choroid thickness after short-term application of 1% atropine gel and its influencing factors in 6-7-year-old children. *Curr Eye Res* 2021;46(8):1171-1177.

31 Zhao WC, Li ZY, Hu Y, Jiang JY, Long W, Cui DM, Chen WY, Yang X. Short-term effects of atropine combined with orthokeratology (ACO) on choroidal thickness. *Cont Lens Anterior Eye* 2021;44(3): 101348.

32 Schmucker C, Schaeffel F. Contrast sensitivity of wildtype mice wearing diffusers or spectacle lenses, and the effect of atropine. *Vision Res* 2006;46(5):678-687.

33 Diether S, Schaeffel F. Long-term changes in retinal contrast sensitivity in chicks from frosted occluders and drugs: relations to myopia? *Vision Res* 1999;39(15):2499-2510.

34 Li FF, Zhang YZ, Zhang XJ, Yip BHK, Tang SM, Kam KW, Young AL, Chen LJ, Tham CC, Pang CP, Yam JC. Age effect on treatment responses to 0.05%, 0.025%, and 0.01% atropine: low-concentration atropine for myopia progression study. *Ophthalmology* 2021;128(8):1180-1187.

35 Yam JC, Jiang YN, Lee J, Li S, *et al*. The association of choroidal thickening by atropine with treatment effects for myopia: two-year clinical trial of the low-concentration atropine for myopia progression (LAMP) study. *Am J Ophthalmol* 2022;237:130-138.

36 Mank JE, Rideout EJ. Developmental mechanisms of sex differences: from cells to organisms. *Development* 2021;148(19):dev199750.

37 Chen ZP, Zhuang YJ, Xu ZX, Chan LYL, Zhang SL, Ye QQ, Feng L, Lu ZL, Li JR. Sensitivity and stability of functional vision tests in detecting subtle changes under multiple simulated conditions. *Transl Vis Sci Technol* 2021;10(7):7.

38 Jiang JY, Long W, Hu Y, Zhao F, Zhao WC, Zheng BR, Feng ZB, Li ZY, Yang X. Accommodation and vergence function in children using atropine combined with orthokeratology. *Cont Lens Anterior Eye* 2023;46(1):101704.

39 Breliant RE, Pang Y, Bandstra A, Kattouf V. Effect of low-dose atropine on binocular vision and accommodation in children aged 6 to 17 years. *Optom Vis Sci* 2023;100(8):550-556.

40 Xu HN, Ye LY, Peng YJ, *et al*. Potential choroidal mechanisms underlying atropine's antimyopic and rebound effects: a mediation analysis in a randomized clinical trial. *Invest Ophthalmol Vis Sci* 2023;64(4):13.