Measuring changes in Schlemm's canal and trabecular meshwork in different accommodation states in myopia children: an observational study

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Measuring Changes of Schlemm's Canal and Trabecular Meshwork in Different Accommodation States in Myopic Children: an observational study

Running title: SC and TM size in different Accommodation states

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Conflict of interest statement

The work is original, and there is no conflict of interest to disclose

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Abstract

Purpose: Studies were designed to evaluate changes in the size of the Schlemm's Canal (SC) and trabecular meshwork(TM) during accommodation stimuli and cycloplegia states in myopic children.

Methods: 34 children were enrolled. A -6D accommodation stimulus was achieved by looking at an optotype through a mirror. Cycloplegia state was induced with 1% tropicamide. Two states were confirmed by measuring the central lens thickness（CLT）, the anterior chamber depth and the pupil diameter. The size of the Schlemm's Canal (SC) and Trabecular Meshwork(TM) was measured using swept-source optical coherence tomography. And the associations between the change of the SC and the CLT were analyzed.

Results: When compared with the relaxation state, under -6D accommodation stimuli, the size of SC increased significantly: the SC area (SCA) amplified from 6371±2517μm^2 to 7824±2727 μm^2; the SC length (SCL) from 249±10 μm to 295±12 μm, and SC width (SCW) from 27±9 μm to 31±8 μm. Under cycloplegia state, the SCA reduced to 5009±2028 μm^2; the SCL to 212±μm and the SCW to 22±5 μm. In addition, the changed areas of SCA (r=0. 35; P=0.0007), SCL (r=0. 251; P=0.0172), and SCW (r=0. 253; P=0.016) were significantly correlated with the change in CLT. However, the size of TM did not change substantially when compared with the relaxation state. Only the TM length (TML) increased from 562±45μm to 587±47μm after -6D accommodation stimulus.

Conclusion: SC size enlarges after -6D accommodation stimuli and shrinks under

cycloplegia. However, for TM, only the TM length increase under accommodation stimulus state.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide and its incidence is high. It is also acknowledged that elevated intraocular pressure (IOP) is the major risk factor for glaucoma, which appears to result from increased resistance to aqueous humor outflow. Trabecular meshwork (TM) and Schlemm's canal (SC) are the key structures related to aqueous humor flow pathways[1, 2]. Clinically, surgical or pharmacological treatments targeting SC and TM could alleviate elevated IOP [3] . Therefore, SC and TM have been considered as promising therapeutic targets for the treatment of glaucoma. Researchers reported that accommodation stimulation promotes aqueous humor outflow facility and decreases IOP [4-6]. On the other hand, paralysis of accommodation with cycloplegia raises the aqueous outflow resistance and the IOP[7, 8]. The possible mechanisms underlying these changes are unclear. Most researchers suggest that the mechanical effect of the ciliary muscle under different accommodation states mediates the TM and SC structural changes. However, to date, the effects of accommodation on the structural changes of SC and TM have not been observed in vivo for humans. Currently, the optical coherence tomography (OCT) provides a non-invasive cross-sectional imaging technique of the eye and produces static and dynamic anterior segment images. Besides, myopia is a known risk factor especially for primary open-angle glaucoma[9, 10]. The aim of this study is to explore changes in TM and SC structures of different accommodation states (accommodation stimulus, relaxation of accommodation and paralysis of accommodation) in myopic patients by the adoption of OCT imaging as this could benefit our understanding of glaucoma.

Methods:

Ethics approval was obtained from the local Institute's Ethical Committee (Huazhong University of Science and Technology) and the study protocol registered with chictr.org.cn (ChiCTR-ROC-16008832).Written informed consent was obtained from parents. In total, 34 children at a refraction outpatient clinic of Tongji hospital were recruited to the study during a period of 4 months between June and September, 2017. Children were aged from 7 to 14 years old and suffered from refractive error (⩾-6D and⩽−0.5D, corrected visual acuity of at least 20/20 in Snellen equivalent), and needed cycloplegic refraction testing. The exclusion criteria were: (i) presence or history of other ocular diseases, (ii) the amplitude of accommodation of subjects less than 6.0 D and (iii) the presence of central nervous system or systemic diseases.

Experimental procedure:

Serial regular ocular examinations were performed to screen patients with ocular diseases other than refractive error: these include slit lamp, fundus examination, IOP, axial length check and subjective optometry. Afterwards, amplitude of accommodation was measured using minus lens test as reported by León [11] and patients were excluded if their accommodation amplitude was less than 6D.

Then patients were asked to undergo an OCT test. The first test was under the relaxation state accommodation, which was achieved by far point staring. Next, subjects were tested under the -6D accommodation stimulate state. This state was achieved by watching mirrored optotypes, which were placed at a distance calculated for each individual based on the formula: 100/-(-6+X) cm (X was the patient's refractory error value in diopters). Lastly subjects were tested under the state of cycloplegia. This was done by giving patients 1% tropicamide eye drops on the cornea surface 5 times with a 5 minute interval in each eye and measurements were made 5 minutes after the last drops of tropicamide.

Outcome measures: OCT Data Acquisition and Processing

The primary outcome measure in this study was the SC area (SCA) of different accommodation states. Participants underwent examinations of swept-source optical coherence tomography (OCT) (CASIA SS-1000; Tomey Corporation, Nagoya, Japan), which is specifically designed for anterior segment imaging using a 1310nm wavelength with a scan speed of 30,000 A-scans per second and an axial resolution of less than 10 μ m. To enable measurements of different states, we did as Esteve-Taboada reported[12] by using a tilted first surface mirror to fix stimulus at different vergences in the left eye. The tilted mirror with a frame carrying a rotation axis was fixed to the OCT machine (see simulated diagram, Fig. 1A). Subjects were asked to look at optotypes in the mirror with the left eye while measurements were taken on the right eye. Researchers adjusted the tilting angle of the mirror for every patient according to the particular interpupillary distance, testing items and side. Subjects were instructed to look at an optotype through the tilted mirror and the optotype was placed at the required distance (far point for the relaxation and cycloplegic states, an individually calculated distance for the -6D accommodation state). The angle analysis mode (dimension, a raster of 128B-scans each with 512 A-scans over 8 mm) was used to capture images of the ACD, PD and CLT. Then, the 3D-angle high-definition mode (dimension, a raster of 64 B-scans each with 512 A-scans over 8 mm) was chosen to capture images of the SC, TM and ciliary muscle 9 o'clock positions and conjunctival vessels were used as landmarks to scan the same site under different states. During the image acquisition, blinking was not permitted and each measurement was taken 4s later since the patient's last blink allowed the tear film to spread over the cornea.

Figure 1 about here

Image analysis

Each image was quantified manually using the Image J software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). Measuring items were determined based on two-dimensional images (example of measure items in Fig1B-F). The anterior chamber depth (ACD) was defined as the perpendicular distance between the corneal endothelium at the corneal apex to the anterior lens surface while the central lens thickness (CLT) was the distance of the midpoint of the front and back of the crystal lens. The pupil diameter (PD) was perceived as the distance between the edges of the iris whereas the scleral spur was the point between the TM and the ciliary body. Thickness of the ciliary muscle at 2(CM2) and 3 (CM3) mm posterior to the scleral spur was assessed (Limited by OCT scan depth, we did not analyze the data of the ciliary muscle width at 1mm posterior to the scleral spur). The SC area was drawn freehand and depicted the area surrounded by the outline of the SC. The SC length was measured from the posterior to the anterior SC end point. The SC width was calculated by taking the two average values of one third points. The TM length was regarded as the distance between the scleral spur and the Schwalbe's line. According to our previous reports[13, 14], each TM width measurement was made perpendicular to the inner layer of the meshwork. The TM width was calculated as the average of two measurements made at the anterior end point of SC and halfway down the SC.

Quality control

Researchers were trained before conducting the study. All measurements were taken by a skilled operator who was blinded to treatments and the scans of each site were repeated three times. The ambient lighting conditions were kept constant during the whole procedure in order not to have significant variations in the pupil diameter. The right eye of each subject was selected for OCT scanning while the left eye was used for vergence. All measurement items were sequentially taken in three different accommodation conditions (-6D accommodation, relaxation and cycloplegia situation). The images of these eyes were evaluated by two observers independently who were blinded to treatments as before[14]. To measure intraobserver repeatability, each image was measured by one observer two separate times at an interval of 3 days, and agreement between the two observations was analyzed. To measure interobserver reproducibility, the same images were evaluated by two observers, and the agreement between them was determined. The intraclass correlation coefficients were calculated using a two-way mixed effect model.

Statistical Analyses

The results were evaluated using the SPSS software package version19.0 (IBM Corp., Armonk, NY, USA). Sample size estimation was based on the assumption that there is a difference in SCA between different accommodation states. We computed the sample size needed for a repeated measures analysis of variance (rANOVA). A medial level of partial eta square of 0.06 was adopted, which gave an effect size of about 0.25. A sample size of at least 28 participants was deemed to be sufficient to give us a power of 0.80 with 95% confidence. The final sample size was adjusted to 34 based on the 20% participant loss. Quantitative data are presented as mean ± standard deviation. Repeat measure ANOVA was performed to reveal significant differences between different accommodation states. Prior to the repeat measure ANOVA, the sphericity assumption was checked using the Mauchly's sphericity test. And when the sphericity test was not statistically significant, the Greenhouse-Geisser correction was applied. The Bonferroni procedure was used as a post hoc test for comparisons between groups and $P < 0.05$ was set as statistical significance in all cases.

Results:

A total of 34 children, aged from 7 to 14 years were recruited. Four were excluded due to poor patient cooperation or low quality of the OCT images. Thus, a total of 30 patients (16 male; 14 female) were eventually included in the analyses. The mean values for various variables were: patient age 12.07±2.27 years, best corrected visual acuity 1.08±0.12, AL 24.61±1.33mm, the refraction –3.05±2.53 diopters, intraocular pressure 15.24±2.65mmHg and the amplitude of accommodation 10.23±2.12 diopters.

1. Accommodation state changes achieved by accommodation stimulus or cycloplegia

To determine whether artificial accommodation states have been established, we tested the changes of the central lens thickness (CLT), anterior chamber depth (ACD) and pupil diameter (PD). There were significant differences between different accommodation states (F_{CLT}=112.9, P_{CLT}=0.00; F_{ACD}=153.8, P_{ACD}=0.00; F_{PD}=271.4, P_{PD}=0.00). When given -6D accommodation stimulation, the CLT increased (from 3.62±0.17mm to 3.89±0.24mm, P<0.001), while ACD (from 3.28±0.23mm to 3.09±0.26mm, P<0.001) and PD (from 5.71±0.86mm to 4.62±0.73mm, P<0.001) decreased. Under the state of cycloplegia with tropicamide, the CLT reduced (from 3.62±0.17mm to 3.57±0.15mm, P<0.001), whereas the ACD (from 3.28±0.23mm to 3.35±0.22mm, P<0.001) and the PD (from 5.71±0.86mm to 7.90±0.51mm, P<0.001) increased (Fig2).

Figure 2 about here

2. Ciliary muscle thickness (include CM2, CM3) in different accommodation

of the eye.

We also observed the thickness of ciliary body muscles in different accommodation states. Two sites of the ciliary muscle which are 2mm and 3mm distance from the Scleral spur were tested. Ciliary muscle thickness changed at CM2 ($F=12.9$, $P=0.00$) and CM3 ($F=25.0$, $P=0.00$). When compared with the basal state, the 2mm distance from the Scleral spur of the ciliary muscle increased under the cycloplegia state (496±*69*μm *vs* 468±*69*μm, $P<0.05$) but not under the accommodation stimulus (454±*64*μm *vs*468±*69*μm, $P>0.05$) (Fig 3). The thickness of the ciliary muscle at 3mm distance from the Scleral spur decreased under the accommodation stimulus (271±*8*μm *vs* 292±*8*μm, $P<0.05$) and increased under the cycloplegia state (310±*8*μm *vs*292±*8*μm, $P<0.05$).

Figure 3 about here

3. Schlemm's Canal changed in different accommodation states of the eye

We evaluated the changes of the Schlemm's Canal by measuring its area, length and width. After-6D accommodation or cycloplegia with tropicamide was given, when compared with the relaxation state, the mean values of SCA ($F=10.959$; $P < 0.05$), SCL ($F=8.345$; $P < 0.05$) and SCW ($F=5.107$; $P < 0.05$) were found to have significantly changed. After -6D accommodation stimulation, the SCA increased on average by 22.80% (7824±2727 μm^2 VS 6371±2517μm^2, $P < 0.05$), the SCL by 18.76% (295±12 μm VS 249±10 μm, $P < 0.05$) and the SCW by16.53% (31±8 μm VS

27±9 μm P <0.05). However, after cycloplegia with 1% tropicamide, the SCA decreased on average by 21.37% (5009±2029 μm^2 VS 6371±2517μm^2, $P < 0.05$), the SCL by 14.76% (212±14μm VS 249±10 μm, $P < 0.05$) and the SCW by 17.90% (22±5 μm VS 27±9 μm, $P < 0.05$) (Fig5). In addition, the changed areas of SCA (r = 0. 35; P = 0.0007), SCL (r = 0. 251; P = 0.0172), and SCW (r = 0. 253; P = 0.016) were significantly correlated with the change in CLT (Fig4).

Figure4 about here

4. Trabecular meshwork changed in different accommodation states of the eye

We evaluated the changes of trabecular meshwork by measuring its length and width. TM width was found to have made no significant changes in different accommodation states (F=2.48， P=0.92), but TM length changed considerably (F=15.8, P= 0.00). When compared with the basal level, TM length increased on average by 4.49% (587±46μm VS 562±45μm, P<0.05) after -6D accommodation stimulus. However, it did not change after cycloplegia with tropicamide (Fig5).

Figure 5 about here

Discussion:

This study, to our knowledge, is the first in vivo study reporting the effects of different accommodation states in human TM and SC structural changes in myopic patients. These findings will provide a more reliable and trusted message to our understanding of the mechanisms of IOP regulation, the aqueous humor outflow. The outcome is also beneficial to understanding the mechanism of glaucoma.

In the present study, myopic children were recruited since they needed cycloplegia for optometry and there was no burden for additional pharmacological intervention. Two artificial accommodation states were established. Paralysis of accommodation was achieved by tropicamide which is normally used in clinics and already known to be safe when used in children with myopia. Accommodation stimulus was achieved as reported by Ferrer Blasco [12]. To verify these two artificial accommodation states, parameters associated with accommodation, including central lens thickness (CLT), anterior chamber depth (ACD) and pupil diameter (PD) were tested. As expected, the CLT increased after -6D accommodation stimulation but decreased following cycloplegia. On the other hand, the ACD and PD decreased after -6D accommodation stimulation whereas it increased after cycloplegia with tropicamide. Thus two typical artificial accommodation states were established in myopia children as previously reported[12, 15, 16].

Ciliary body muscles change with accommodation. The change of CM provides direct evidence of accommodation stimulation and cycloplegia. There are researches which have explored changes in the ciliary muscle structure with accommodation using UBM, MRI and OCT[17-21]. The results indicate that the shape change occurred in the anterior portion of the ciliary muscle with accommodation. Ciliary muscle thickness at 1mm posterior to the scleral spur increased with accommodation but thinned at CM2, CMT3. In our study, due to limitation of the OCT scan depth, we only analyzed changes at CM2 and CM3 and found that their thickness decreased after -6D accommodation stimulation. And our results are consistent with other studies[17, 18].

In this study, we found that the SC structure significantly changed under different accommodation states: the SC area increased on average about 22.80%, the SC length by 18.76% and the SC width by 16.53% after -6D accommodation stimulation. On the other hand, after cycloplegia with 1% tropicamide, the area of SC decreased on average by 21.37%, the SC length by 14.76% and the SC width by 17.90%. Earlier studies have shown that accommodation stimulation or pilocapine can decrease the aqueous humor outflow resistance and lower the IOP[4, 5, 22]. Paradoxically, cycloplegia increased the aqueous humor outflow resistance in monkeys, normal people and POAG patients[7, 8]. The reason of the IOP change is totally unclear. However, we could speculate that this is possibly due to the change of the SC structure, mainly the inner wall of SC and the juxtacanalicular tissue (JCT), which are the major sources of aqueous humor outflow resistance, under different accommodation states. The power of accommodation derived from ciliary muscle contraction includes the longitudinal and circular ciliary muscles. The longitudinally ciliary muscle is directly connected to the scleral spur in human eyes[23, 24]. Thus, when the ciliary muscle contracts during the accommodation state, it also can posteriorly and internally pull the sclera spur, which produces the widening of the spaces between the corneoscleral trabecular and the distension of the outer and endothelial meshwork, and thus increase the giant vacuoles into the SC [25]. The ciliary muscle tendon has elastic-like fibers called the cribriform plexus which directly connect to the inner endothelial wall of the Schlemm's canal[26]. The ciliary muscle tone can therefore, directly influence the Schlemm's canal inner wall and JCT structure through the fiber system of the cribriform plexus[26, 27].

Trabecular meshwork, another important structure in the aqueous humor outflow, however, did not change significantly in size after -6D accommodation stimulation and cycloplegia. Only the TM length increased slightly on average by 4.49% after -6D accommodation stimulus. We speculate that maybe TM also possesses the ability to contract. Wiederholt et al found a direct role of trabecular meshwork contractility in aqueous outflow regulation[28]. The researchers showed that TM contains cholinergic innervation nerve terminals and α -smooth muscle actin positive cells in bovine, mice and primates[1, 29]. In vitro perfusion of the anterior segments (without ciliary muscle) with cholinergic agonist (pilocapine) could induce contraction of the TM and decrease the outflow facility[30]. However, when pilocapine is applied to the entire eye of the ciliary muscle, the outflow facility increased both in mice and primates[1, 31]. This evidence indicates that TM and the ciliary muscle are not connected in the same way. Although under the accommodation stimulation, TM could be pulled by the ciliary body. However, contraction of TM itself could offset the stretching effect of the ciliary muscle on TM.

There are some limitations in this study. First, we only observed SC and TM changes under the -6D accommodation stimuli, but not a step-by-step accommodation (from-2D to -6D). A more detailed assessment of the accommodation states could provide additional information for daily life situations such as reading, which usually needs 2-4D accommodation and already demonstrated IOP lowering. Second, we only tested myopic patients. Whether there is a difference in healthy people or other cases needs further study. Third, this study is limited to children, who are likely to have more compliant tissues. For adults, the effect would likely be smaller and need further study to confirm.

In conclusion, SC size enlarges after -6D accommodation stimuli and shrinks after cycloplegia. However, for TM, only the TM length increases under accommodation stimulus state. These may reveal the reason why IOP decreased after accommodation and help to characterize the underlying pathophysiological mechanisms involved in the regulation of IOP and glaucoma.

Conflict of interest statement

The work is original, and there is no conflict of interest to disclose.

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Figure legend:

Fig1. Simulated diagram of experimental set-up and examples of the measured items in OCT image. A: A tilted first-surface mirror with a frame carrying a rotation axis was attached to the OCT machine and used to place the fixation stimulus at different vergences. Measurements were taken on the right eye of the subject while the left eye looked at an optotype through the mirror. Pictures show the simulated diagram (left), the whole view of our testing system (middle) and the large view of optotype in the mirror (right). B: Simulated diagram of the anterior eye segment accounting for the measured items in this study: Central Lens Thickness (CLT), Pupil Diameter (PD), Schlemm’s canal length(SCL), Schlemm’s canal width (SCW), trabecular meshwork length (TML), trabecular meshwork width (TMW), ciliary muscle 2 (CM2) and 3 (CM3) mm posterior to the scleral spur，scleral spur （SS）. C: OCT image shows the measured CLT, PD. D: OCT image shows the measured ACD. E: OCT image shows the measured Schlemm’s canal (yellow loop, including SCL and SCW) and the trabecular meshwork (green arrow, including TML and TMW). F: Image shows the measured ciliary muscle (Yellow line respectively marked the testing site of CM2 and CM3).

Fig2: The central lens thickness (CLT), anterior chamber depth（ACD）and pupil diameter（PD） in different accommodation states of the eye. A&D: Example of CLT, ACD and PD in the -6D accommodation state; B&E: Example of CLT, ACD and PD in the relaxation state; C&F: Example of CLT, ACD and PD in the cycloplegia state; G-I: Statistical graph of CLT, ACD and PD in different accommodation states (**P<0.01).

Fig3: Ciliary muscle thickness in different accommodation states of the eye. A-B: Respectively showing 2mm and 3mm posterior to the scleral spur (**P<0.01, * P<0.05).

Fig4. Schlemm’s Canal changes in different accommodation states. A&D: Typical OCT image of the Schlemm’s Canal and trabecular meshwork in the -6D accommodation state; B&E: Typical OCT image of the Schlemm’s Canal and trabecular meshwork in the relaxation state; C&F: Typical OCT image of the Schlemm's Canal and trabecular meshwork in the cycloplegia state; (Scale bar for A-C=500 μm, D-F has the larger view with a scale bar=200 μm). G-I: Statistical graph of SCA, SCL and SCW in different accommodation states (**P<0.01). J-L: Shows the SCA, SCL and SCW changes correlated with the changes in CLT.

Fig5: Trabecular meshwork changes in different accommodation states of the eye. A: Statistical graph of trabecular meshwork width (TMW) in different accommodations of the eye. B: Statistical graph of trabecular meshwork length (TML) in different accommodations of the eye (**P<0.01).