

1 **Measuring Changes of Schlemm’s Canal and Trabecular Meshwork in**
2 **Different Accommodation States in Myopic Children: an observational study**

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4 **Running title:** SC and TM size in different Accommodation states

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23 **Abstract**

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

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

34 Results: When compared with the relaxation state, under -6D accommodation stimuli,
35 the size of SC increased significantly: the SC area (SCA) amplified from
36 $6371\pm 2517\mu\text{m}^2$ to $7824\pm 2727\mu\text{m}^2$; the SC length (SCL) from $249\pm 10\mu\text{m}$ to 295 ± 12
37 μm , and SC width (SCW) from $27\pm 9\mu\text{m}$ to $31\pm 8\mu\text{m}$. Under cycloplegia state, the SCA
38 reduced to $5009\pm 2028\mu\text{m}^2$; the SCL to $212\pm\mu\text{m}$ and the SCW to $22\pm 5\mu\text{m}$. In addition,
39 the changed areas of SCA ($r=0.35$; $P=0.0007$), SCL ($r=0.251$; $P=0.0172$), and SCW
40 ($r=0.253$; $P=0.016$) were significantly correlated with the change in CLT. However,
41 the size of TM did not change substantially when compared with the relaxation state.
42 Only the TM length (TML) increased from $562\pm 45\mu\text{m}$ to $587\pm 47\mu\text{m}$ after -6D
43 accommodation stimulus.

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

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

47 **KEYWORDS:** Schlemm's Canal, Trabecular Meshwork, accommodation

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67 **Introduction**

68 Glaucoma is the leading cause of irreversible blindness worldwide and its
69 incidence is high. It is also acknowledged that elevated intraocular pressure (IOP) is
70 the major risk factor for glaucoma, which appears to result from increased resistance
71 to aqueous humor outflow. Trabecular meshwork (TM) and Schlemm's canal (SC) are
72 the key structures related to aqueous humor flow pathways^{1, 2}. Clinically, surgical or
73 pharmacological treatments targeting SC and TM could alleviate elevated IOP³.
74 Therefore, SC and TM have been considered as promising therapeutic targets for the
75 treatment of glaucoma. Researchers reported that accommodation stimulation
76 promotes aqueous humor outflow facility and decreases IOP⁴⁻⁶. On the other hand,
77 paralysis of accommodation with cycloplegia raises the aqueous outflow resistance
78 and the IOP^{7, 8}. The possible mechanisms underlying these changes are unclear. Most
79 researchers suggest that the mechanical effect of the ciliary muscle under different
80 accommodation states mediates the TM and SC structural changes. However, to date,
81 the effects of accommodation on the structural changes of SC and TM have not been
82 observed in vivo for humans. Currently, the optical coherence tomography (OCT)
83 provides a non-invasive cross-sectional imaging technique of the eye and produces
84 static and dynamic anterior segment images. Besides, myopia is a known risk factor
85 especially for primary open-angle glaucoma^{9, 10}. The aim of this study is to explore
86 changes in TM and SC structures of different accommodation states (accommodation
87 stimulus, relaxation of accommodation and paralysis of accommodation) in myopic
88 patients by the adoption of OCT imaging as this could benefit our understanding of

89 glaucoma.

90 **Methods:**

91 Ethics approval was obtained from the local Institute's Ethical Committee
92 (Huazhong University of Science and Technology) and the study protocol registered
93 with chictr.org.cn (ChiCTR-ROC-16008832). Written informed consent was obtained
94 from parents. In total, 34 children at a refraction outpatient clinic of Tongji hospital
95 were recruited to the study during a period of 4 months between June and September,
96 2017. Children were aged from 7 to 14 years old and suffered from refractive error
97 ($\geq -6D$ and $\leq -0.5D$, corrected visual acuity of at least 20/20 in Snellen equivalent),
98 and needed cycloplegic refraction testing. The exclusion criteria were: (i) presence or
99 history of other ocular diseases, (ii) the amplitude of accommodation of subjects less
100 than 6.0 D and (iii) the presence of central nervous system or systemic diseases.

101 **Experimental procedure:**

102 Serial regular ocular examinations were performed to screen patients with ocular
103 diseases other than refractive error: these include slit lamp, fundus examination, IOP,
104 axial length check and subjective optometry. Afterwards, amplitude of
105 accommodation was measured using minus lens test as reported by León¹¹ and
106 patients were excluded if their accommodation amplitude was less than 6D.

107 Then patients were asked to undergo an OCT test. The first test was under the
108 relaxation state accommodation, which was achieved by far point staring. Next,
109 subjects were tested under the -6D accommodation stimulate state. This state was
110 achieved by watching mirrored optotypes, which were placed at a distance calculated

111 for each individual based on the formula: $100/(-6+X)$ cm (X was the patient's
112 refractory error value in diopters). Lastly subjects were tested under the state of
113 cycloplegia. This was done by giving patients 1% tropicamide eye drops on the
114 cornea surface 5 times with a 5 minute interval in each eye and measurements were
115 made 5 minutes after the last drops of tropicamide.

116 **Outcome measures: OCT Data Acquisition and Processing**

117 The primary outcome measure in this study was the SC area (SCA) of different
118 accommodation states. Participants underwent examinations of swept-source optical
119 coherence tomography (OCT) (CASIA SS-1000; Tomey Corporation, Nagoya,
120 Japan), which is specifically designed for anterior segment imaging using a 1310nm
121 wavelength with a scan speed of 30,000 A-scans per second and an axial resolution of
122 less than $10\ \mu\text{m}$. To enable measurements of different states, we did as Esteve-
123 Taboada reported¹² by using a tilted first surface mirror to fix stimulus at different
124 vergences in the left eye. The tilted mirror with a frame carrying a rotation axis was
125 fixed to the OCT machine (see simulated diagram, Fig. 1A). Subjects were asked to
126 look at optotypes in the mirror with the left eye while measurements were taken on
127 the right eye. Researchers adjusted the tilting angle of the mirror for every patient
128 according to the particular interpupillary distance, testing items and side. Subjects
129 were instructed to look at an optotype through the tilted mirror and the optotype was
130 placed at the required distance (far point for the relaxation and cycloplegic states, an
131 individually calculated distance for the -6D accommodation state). The angle analysis
132 mode (dimension, a raster of 128B-scans each with 512 A-scans over 8 mm) was used

133 to capture images of the ACD, PD and CLT. Then, the 3D-angle high-definition mode
134 (dimension, a raster of 64 B-scans each with 512 A-scans over 8 mm) was chosen to
135 capture images of the SC, TM and ciliary muscle 9 o'clock positions and conjunctival
136 vessels were used as landmarks to scan the same site under different states. During the
137 image acquisition, blinking was not permitted and each measurement was taken 4s
138 later since the patient's last blink allowed the tear film to spread over the cornea.

139

140 Figure 1 about here

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142 **Image analysis**

143 Each image was quantified manually using the Image J software
144 (<http://imagej.nih.gov/ij/>; provided in the public domain by the National Institutes of
145 Health, Bethesda, MD, USA). Measuring items were determined based on two-
146 dimensional images (example of measure items in Fig1B-F). The anterior chamber
147 depth (ACD) was defined as the perpendicular distance between the corneal
148 endothelium at the corneal apex to the anterior lens surface while the central lens
149 thickness (CLT) was the distance of the midpoint of the front and back of the crystal
150 lens. The pupil diameter (PD) was perceived as the distance between the edges of the
151 iris whereas the scleral spur was the point between the TM and the ciliary body.
152 Thickness of the ciliary muscle at 2(CM2) and 3 (CM3) mm posterior to the scleral
153 spur was assessed (Limited by OCT scan depth, we did not analyze the data of the
154 ciliary muscle width at 1mm posterior to the scleral spur). The SC area was drawn

155 freehand and depicted the area surrounded by the outline of the SC. The SC length
156 was measured from the posterior to the anterior SC end point. The SC width was
157 calculated by taking the two average values of one third points. The TM length was
158 regarded as the distance between the scleral spur and the Schwalbe's line. According
159 to our previous reports^{13, 14}, each TM width measurement was made perpendicular to
160 the inner layer of the meshwork. The TM width was calculated as the average of two
161 measurements made at the anterior end point of SC and halfway down the SC.

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163 **Quality control**

164 Researchers were trained before conducting the study. All measurements were taken
165 by a skilled operator who was blinded to treatments and the scans of each site were
166 repeated three times. The ambient lighting conditions were kept constant during the
167 whole procedure in order not to have significant variations in the pupil diameter.
168 The right eye of each subject was selected for OCT scanning while the left eye was
169 used for vergence. All measurement items were sequentially taken in three different
170 accommodation conditions (-6D accommodation, relaxation and cycloplegia
171 situation). The images of these eyes were evaluated by two observers independently
172 who were blinded to treatments as before¹⁴. To measure intraobserver repeatability,
173 each image was measured by one observer two separate times at an interval of 3 days,
174 and agreement between the two observations was analyzed. To measure interobserver
175 reproducibility, the same images were evaluated by two observers, and the agreement
176 between them was determined. The intraclass correlation coefficients were calculated

177 using a two-way mixed effect model.

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179 **Statistical Analyses**

180 The results were evaluated using the SPSS software package version 19.0 (IBM
181 Corp., Armonk, NY, USA). Sample size estimation was based on the assumption that
182 there is a difference in SCA between different accommodation states. We computed
183 the sample size needed for a repeated measures analysis of variance (rANOVA). A
184 medial level of partial eta square of 0.06 was adopted, which gave an effect size of
185 about 0.25. A sample size of at least 28 participants was deemed to be sufficient to
186 give us a power of 0.80 with 95% confidence. The final sample size was adjusted to
187 34 based on the 20% participant loss. Quantitative data are presented as mean \pm
188 standard deviation. Repeat measure ANOVA was performed to reveal significant
189 differences between different accommodation states. Prior to the repeat measure
190 ANOVA, the sphericity assumption was checked using the Mauchly's sphericity test.
191 And when the sphericity test was not statistically significant, the Greenhouse-Geisser
192 correction was applied. The Bonferroni procedure was used as a post hoc test for
193 comparisons between groups and $P < 0.05$ was set as statistical significance in all
194 cases.

195

196 **Results:**

197 A total of 34 children, aged from 7 to 14 years were recruited. Four were excluded
198 due to poor patient cooperation or low quality of the OCT images. Thus, a total of 30

199 patients (16 male; 14 female) were eventually included in the analyses. The mean
200 values for various variables were: patient age 12.07 ± 2.27 years, best corrected visual
201 acuity 1.08 ± 0.12 , AL 24.61 ± 1.33 mm, the refraction -3.05 ± 2.53 diopters,
202 intraocular pressure 15.24 ± 2.65 mmHg and the amplitude of accommodation
203 10.23 ± 2.12 diopters.

204 **1. Accommodation state changes achieved by accommodation stimulus or** 205 **cycloplegia**

206 To determine whether artificial accommodation states have been established, we
207 tested the changes of the central lens thickness (CLT), anterior chamber depth (ACD)
208 and pupil diameter (PD). There were significant differences between different
209 accommodation states ($F_{CLT}=112.9$, $P_{CLT}=0.00$; $F_{ACD}=153.8$, $P_{ACD}=0.00$; $F_{PD}=271.4$,
210 $P_{PD}=0.00$). When given -6D accommodation stimulation, the CLT increased (from
211 3.62 ± 0.17 mm to 3.89 ± 0.24 mm, $P < 0.001$), while ACD (from 3.28 ± 0.23 mm to
212 3.09 ± 0.26 mm, $P < 0.001$) and PD (from 5.71 ± 0.86 mm to 4.62 ± 0.73 mm, $P < 0.001$)
213 decreased. Under the state of cycloplegia with tropicamide, the CLT reduced (from
214 3.62 ± 0.17 mm to 3.57 ± 0.15 mm, $P < 0.001$), whereas the ACD (from 3.28 ± 0.23 mm to
215 3.35 ± 0.22 mm, $P < 0.001$) and the PD (from 5.71 ± 0.86 mm to 7.90 ± 0.51 mm, $P < 0.001$)
216 increased (Fig2).

217

218 Figure 2 about here

219

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

221 **of the eye.**

222 We also observed the thickness of ciliary body muscles in different
223 accommodation states. Two sites of the ciliary muscle which are 2mm and 3mm
224 distance from the Scleral spur were tested. Ciliary muscle thickness changed at CM2
225 ($F=12.9$, $P=0.00$) and CM3 ($F=25.0$, $P=0.00$). When compared with the basal state,
226 the 2mm distance from the Scleral spur of the ciliary muscle increased under the
227 cycloplegia state ($496\pm 69\mu\text{m}$ vs $468\pm 69\mu\text{m}$, $P<0.05$) but not under the
228 accommodation stimulus ($454\pm 64\mu\text{m}$ vs $468\pm 69\mu\text{m}$, $P>0.05$) (Fig 3). The thickness of
229 the ciliary muscle at 3mm distance from the Scleral spur decreased under the
230 accommodation stimulus ($271\pm 8\mu\text{m}$ vs $292\pm 8\mu\text{m}$, $P<0.05$) and increased under the
231 cycloplegia state ($310\pm 8\mu\text{m}$ vs $292\pm 8\mu\text{m}$, $P<0.05$).

232

233 Figure 3 about here

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

236 We evaluated the changes of the Schlemm's Canal by measuring its area, length
237 and width. After -6D accommodation or cycloplegia with tropicamide was given,
238 when compared with the relaxation state, the mean values of SCA ($F=10.959$; $P <$
239 0.05), SCL ($F=8.345$; $P < 0.05$) and SCW ($F=5.107$; $P < 0.05$) were found to have
240 significantly changed. After -6D accommodation stimulation, the SCA increased on
241 average by 22.80% ($7824\pm 2727 \mu\text{m}^2$ VS $6371\pm 2517\mu\text{m}^2$, $P < 0.05$), the SCL by
242 18.76% ($295\pm 12 \mu\text{m}$ VS $249\pm 10 \mu\text{m}$, $P < 0.05$) and the SCW by 16.53% ($31\pm 8 \mu\text{m}$ VS

243 27±9 μm P <0.05). However, after cycloplegia with 1% tropicamide, the SCA
244 decreased on average by 21.37% (5009±2029 μm² VS 6371±2517μm², P < 0.05), the
245 SCL by 14.76% (212±14μm VS 249±10 μm, P < 0.05) and the SCW by 17.90%
246 (22±5 μm VS 27±9 μm, P < 0.05) (Fig5). In addition, the changed areas of SCA (r =
247 0. 35; P = 0.0007), SCL (r = 0. 251; P = 0.0172), and SCW (r = 0. 253; P = 0.016)
248 were significantly correlated with the change in CLT (Fig4).

249

250 Figure4 about here

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

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

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260 Figure 5 about here

261

262 **Discussion:**

263 This study, to our knowledge, is the first in vivo study reporting the effects of
264 different accommodation states in human TM and SC structural changes in myopic

265 patients. These findings will provide a more reliable and trusted message to our
266 understanding of the mechanisms of IOP regulation, the aqueous humor outflow. The
267 outcome is also beneficial to understanding the mechanism of glaucoma.

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

281 Ciliary body muscles change with accommodation. The change of CM provides
282 direct evidence of accommodation stimulation and cycloplegia. There are researches
283 which have explored changes in the ciliary muscle structure with accommodation using
284 UBM, MRI and OCT¹⁷⁻²¹. The results indicate that the shape change occurred in the
285 anterior portion of the ciliary muscle with accommodation. Ciliary muscle thickness at
286 1mm posterior to the scleral spur increased with accommodation but thinned at CM2,

287 CMT3. In our study, due to limitation of the OCT scan depth, we only analyzed changes
288 at CM2 and CM3 and found that their thickness decreased after -6D accommodation
289 stimulation. And our results are consistent with other studies^{17, 18}.

290 In this study, we found that the SC structure significantly changed under different
291 accommodation states: the SC area increased on average about 22.80%, the SC length
292 by 18.76% and the SC width by 16.53% after -6D accommodation stimulation. On the
293 other hand, after cycloplegia with 1% tropicamide, the area of SC decreased on
294 average by 21.37%, the SC length by 14.76% and the SC width by 17.90%. Earlier
295 studies have shown that accommodation stimulation or pilocarpine can decrease the
296 aqueous humor outflow resistance and lower the IOP^{4, 5, 22}. Paradoxically, cycloplegia
297 increased the aqueous humor outflow resistance in monkeys, normal people and
298 POAG patients^{7, 8}. The reason of the IOP change is totally unclear. However, we
299 could speculate that this is possibly due to the change of the SC structure, mainly the
300 inner wall of SC and the juxtacanalicular tissue (JCT), which are the major sources of
301 aqueous humor outflow resistance, under different accommodation states. The power
302 of accommodation derived from ciliary muscle contraction includes the longitudinal
303 and circular ciliary muscles. The longitudinally ciliary muscle is directly connected to
304 the scleral spur in human eyes^{23, 24}. Thus, when the ciliary muscle contracts during the
305 accommodation state, it also can posteriorly and internally pull the sclera spur, which
306 produces the widening of the spaces between the corneoscleral trabecular and the
307 distension of the outer and endothelial meshwork, and thus increase the giant vacuoles
308 into the SC²⁵. The ciliary muscle tendon has elastic-like fibers called the cribriform

309 plexus which directly connect to the inner endothelial wall of the Schlemm's canal²⁶.

310 The ciliary muscle tone can therefore, directly influence the Schlemm's canal inner
311 wall and JCT structure through the fiber system of the cribriform plexus^{26, 27}.

312 Trabecular meshwork, another important structure in the aqueous humor outflow,
313 however, did not change significantly in size after -6D accommodation stimulation
314 and cycloplegia. Only the TM length increased slightly on average by 4.49% after -
315 6D accommodation stimulus. We speculate that maybe TM also possesses the ability
316 to contract. Wiederholt et al found a direct role of trabecular meshwork contractility
317 in aqueous outflow regulation²⁸. The researchers showed that TM contains cholinergic
318 innervation nerve terminals and α -smooth muscle actin positive cells in bovine, mice
319 and primates^{1, 29}. In vitro perfusion of the anterior segments (without ciliary muscle)
320 with cholinergic agonist (pilocarpine) could induce contraction of the TM and decrease
321 the outflow facility³⁰. However, when pilocarpine is applied to the entire eye of the
322 ciliary muscle, the outflow facility increased both in mice and primates^{1, 31}. This
323 evidence indicates that TM and the ciliary muscle are not connected in the same way.
324 Although under the accommodation stimulation, TM could be pulled by the ciliary
325 body. However, contraction of TM itself could offset the stretching effect of the
326 ciliary muscle on TM.

327 There are some limitations in this study. First, we only observed SC and TM
328 changes under the -6D accommodation stimuli, but not a step-by-step accommodation
329 (from -2D to -6D). A more detailed assessment of the accommodation states could
330 provide additional information for daily life situations such as reading, which usually

331 needs 2-4D accommodation and already demonstrated IOP lowering. Second, we only
332 tested myopic patients. Whether there is a difference in healthy people or other cases
333 needs further study. Third, this study is limited to children, who are likely to have
334 more compliant tissues. For adults, the effect would likely be smaller and need further
335 study to confirm.

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

341

342 **Conflict of interest statement**

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

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468 **Figure legend:**

469 Fig1. Simulated diagram of experimental set-up and examples of the measured
470 items in OCT image. A: A tilted first-surface mirror with a frame carrying a rotation
471 axis was attached to the OCT machine and used to place the fixation stimulus at
472 different vergences. Measurements were taken on the right eye of the subject while
473 the left eye looked at an optotype through the mirror. Pictures show the simulated
474 diagram (left), the whole view of our testing system (middle) and the large view of
475 optotype in the mirror (right). B: Simulated diagram of the anterior eye segment
476 accounting for the measured items in this study: Central Lens Thickness (CLT), Pupil
477 Diameter (PD), Schlemm's canal length(SCL), Schlemm's canal width (SCW),

478 trabecular meshwork length (TML), trabecular meshwork width (TMW), ciliary
479 muscle 2 (CM2) and 3 (CM3) mm posterior to the scleral spur, scleral spur
480 (SS) . C: OCT image shows the measured CLT, PD. D: OCT image shows the
481 measured ACD. E: OCT image shows the measured Schlemm's canal (yellow loop,
482 including SCL and SCW) and the trabecular meshwork (green arrow, including TML
483 and TMW). F: Image shows the measured ciliary muscle (Yellow line respectively
484 marked the testing site of CM2 and CM3).

485

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

492

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

496

497 Fig4. Schlemm's Canal changes in different accommodation states. A&D: Typical
498 OCT image of the Schlemm's Canal and trabecular meshwork in the -6D
499 accommodation state; B&E: Typical OCT image of the Schlemm's Canal and

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

505

506 Fig5: Trabecular meshwork changes in different accommodation states of the eye.

507 A: Statistical graph of trabecular meshwork width (TMW) in different
508 accommodations of the eye. B: Statistical graph of trabecular meshwork length
509 (TML) in different accommodations of the eye (**P<0.01).