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Quantitative Analysis of internal components of the human crystalline lens during accommodation in adults

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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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1 **Abstract:**

2 **Objectives.** To quantitatively analyze changes in the inner components of the
3 human crystalline lens during accommodation in adults.

4 **Methods.** Eyes of 23 subjects were sequentially examined using CASIA2 Optical
5 Coherence Tomography under 0D, -3D and -6D accommodation states. The anterior
6 chamber depth (ACD), anterior and posterior crystalline lens radius of the curvature
7 (ALRC and PLRC) were obtained using built-in software. The lens thickness (LT),
8 lenticular nucleus thickness (NT), anterior cortex thickness (ACT), posterior cortex
9 thickness (PCT), anterior and posterior lenticular nucleus radius of the curvature
10 (ANRC and PNRC), anterior and posterior lenticular nucleus vertex (ANV and PNV)
11 were quantified manually with the Image-pro plus software.

12 **Results.** During accommodation, the ACD became significantly shallower and LT
13 significantly increased. For changes in the lens, the ALRC decreased by an average
14 magnitude (related to accommodative stimuli) 0.44 mm/D, and PLRC decreased
15 0.09 mm/D. There was no difference for the ACT and PCT in different accommodation
16 states. For lenticular nucleus response, NT increased on average by 30 μ m/D. Both the
17 ANRC and PNRC decreased on average by 212 μ m/D and 115 μ m/D respectively. The
18 ANV moved forward on average by 0.07mm under -3D accommodative stimuli and
19 0.16mm for -6D. However, there was no statistically significant difference between
20 different accommodation states in the PNV movement.

21 **Conclusion.** Under accommodation stimulation, lens thickness changed mainly
22 due to the lenticular nucleus, but not the cortex. For the lenticular nucleus, both the

23 ANRC and PNRC decreased and ANRC changed the most. The anterior surface of the
24 nucleus moved forward while the posterior surface of the nucleus moved backward
25 but only slightly.

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27 **Keywords:** crystalline lens, lenticular nucleus, lenticular cortex, accommodation

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45 **Introduction:**

46 Accommodation is the ability to provide clear vision during near tasks by
47 increasing the refractive power mainly through crystal lens changes. As accommodation
48 ability decreases and the crystalline hardens, presbyopia often occurs in middle age.
49 And the change in stiffness of the lens material is thought to be responsible for
50 presbyopia. Recently, interest has focused on developing surgical treatments that restore
51 accommodation, including lens photodisruption [1] and lens refilling [2-4]. To fully
52 understand the mechanism of accommodation and clarify the function of the internal
53 structure of the lens during accommodation is very important for developing effective
54 therapeutic strategies. In particular, the nuclear core and the cortex of the lens have
55 distinct different properties[5] and many details about the dynamic optomechanical
56 response of the internal structure of the lens under accommodation stimuli have yet to
57 be quantified.

58 Technologies of slit-lamp photography [6-8], Scheimpflug photography [9] were
59 used to measure the change in the internal structure of the lens during accommodation.
60 However, there are several limitations to these technologies. Firstly, stimulation was on
61 the fellow eye but not directly on the testing eye in these two testing modalities.
62 Secondly, to avoid light effects on the pupil, lens images were obtained on pupil
63 pharmacological dilation, but not on physiological status [8]. Thirdly, images from
64 these early techniques presented relatively lower resolution than modern Optical
65 coherence tomography (OCT) techniques [10].

66 OCT is a low-coherence, interferometry-based imaging modality that provides a

67 high-resolution, noncontact, noninvasive cross sectional image of the anterior segment
68 [11]. The CASIA 2 OCT (Tomey, Nagoya, Japan) can produce a higher sensitivity
69 for depth, axial and transverse spatial resolution with lateral dimension measuring 16
70 mm and axial depth 13 mm. This enables data to be obtained from the cornea to the
71 posterior lens in one image and identifying the capsule, cortex and nucleus of lens.
72 Thus, it is the excellent technology for imaging the internal component of crystalline
73 lens during accommodation in vivo. Further, its built-in programs provide the required
74 accommodative stimulation and the individual precise refractive error correction
75 including correcting astigmatism. Previous research [12-14] has shown that CASIA2
76 OCT can provide good reproducible measurements of lens biometry in both static and
77 dynamic states. In addition, CASIA2 can correct the optical distortion produced by
78 the cornea, aqueous humor and lens with a homogeneous refractive index included in
79 their built-in program [13, 14], which can obtain accurate anterior and posterior lens
80 component shapes. Therefore, the purpose of the present investigation is to measure
81 changes in the internal component of the crystalline eye lens at different
82 accommodation states with the CASIA2 OCT.

83 **Results:**

84 A total of 23 adults aged between 30 and 40 years old were recruited. One was
85 excluded due to low accommodation amplitude of less than -6D. Thus, a total of 22
86 subjects (12males; 10 female) were eventually included in the analyses. The mean
87 values for various variables across subjects were as follows: age, 34.0 ± 2.2 years;
88 refraction, -1.6 ± 0.5 diopters; intraocular pressure, 16.6 ± 2.6 mmHg; and amplitude of

89 accommodation, 9.1 ± 2.1 diopters. During accommodation, neither angle to angle
90 distance (ATA) nor corneal thickness (CT) changed, indicating that movement of eye
91 between scans is negligible ($F_{ATA}=2.58, P=0.11$; $F_{CT}=1.35, P=0.27$).

92 **The changes of the lens shape during accommodation:**

93 During accommodation, the anterior chamber depth (ACD) became significantly
94 smaller while the lens thickness (LT) significantly increased (ANOVA, $F_{LT}=160.69$,
95 $P_{LT}=0.000$; $F_{ACD}=118.89$, $P_{ACD}=0.000$; Fig. 2A,B). With -6D accommodation
96 stimulation, LT increased from 3.85 ± 0.20 mm to 4.03 ± 0.19 mm. For all subjects, both
97 the anterior and posterior crystalline lens radius of curvature (ALRC and PLRC)
98 became smaller during accommodation: ALRC decreased on average 0.44 mm/D to
99 accommodative stimuli, from 11.02 ± 1.72 mm to 9.75 ± 1.16 mm for -3D, and to
100 8.38 ± 0.84 mm for -6D ($F_{ALRC}=100.01$, $P_{ALRC}=0.000$, Fig. 2C), PLRC decreased on
101 average 0.09 mm/D, from 6.00 ± 0.63 mm to 5.77 ± 0.45 mm for -3D, and to 5.49 ± 0.32 mm
102 for -6D ($F_{PLRC}=23.39$, $P_{PLRC}=0.000$, Fig. 2D).

103 **The changes of the lens components during accommodation:**

104 In the resting state eye, the average nucleus thickness (NT) was 2.50 ± 0.16 mm, the
105 anterior cortex thickness (ACT) was 0.51 ± 0.03 mm and the posterior cortex thickness
106 (PCT) 0.84 ± 0.12 mm. When accommodation stimulation was given, the NT increased
107 to 2.57 ± 0.15 mm under -3D and to 2.68 ± 0.14 mm under -6D stimulation, with an
108 average of $30 \mu\text{m/D}$ to accommodative stimuli ($23 \mu\text{m/D}$ for 0 to -3D and $37 \mu\text{m/D}$ for -
109 3 to -6D, $F_{NT}=92.71$, $P=0.000$, Fig 3A). There was no difference of ACT and PCT
110 between different accommodation states ($F_{ACT}=0.42$, $P_{ACT}=0.659$; $F_{PCT}=2.73$,

111 $P_{PCT}=0.077$, Fig3B.C). Representative OCT images for these changes under different
112 accommodative states are shown in figure 4 (from a 35-year-old male with -1.5D
113 myopia).

114 **The changes in lenticular nucleus curvature and position during**
115 **accommodation:**

116 In the resting state eye, the average anterior lenticular nucleus radius of the curvature
117 (ANRC) ranged from 2.53 to 8.1mm (on average 4.06 ± 1.40 mm) while the posterior
118 lenticular nucleus radius of the curvature (PNRC) ranged from 2.26 to 4.67mm (on
119 average 3.26 ± 0.71 mm). When accommodation stimulation was given, both the ANRC
120 and PNRC clearly decreased ($F_{ANRC}=58.25$, $P_{ANRC}=0.000$; $F_{PNRC}=19.75$, $P_{PNRC}=0.000$,
121 Fig5A.B).The ANRC decreased to 3.32 ± 1.00 mm for -3D stimulation and to
122 2.30 ± 0.75 mm for -6D, at a speed of $212 \mu\text{m/D}$ related to accommodative stimuli. In
123 addition, the PNRC decreased to 2.97 ± 0.58 mm for -3D stimulation and to
124 2.57 ± 0.46 mm for -6D, at a speed of $115 \mu\text{m/D}$. To investigate displacement of the
125 nucleus, we measured the anterior and posterior lenticular nucleus vertex (ANV and
126 PNV). The ANV significantly moved forward ($F_{ANV}=107.28$, $P_{ANV}=0.000$, Fig5C),
127 which changed from 4.00 ± 0.27 mm to 3.93 ± 0.25 mm for -3D, and 3.84 ± 0.26 mm for -
128 6D. However, there was no difference between different accommodation states for the
129 PNV movement ($F_{PNV}=1.54$, $P_{PNV}=0.231$ Fig5D).

130 **Discussion:**

131 In this study we assessed changes in the lens internal components during
132 accommodation in vivo using the CASIA2 OCT. Measuring the exact changes in the

133 human crystalline lens during accommodation is very important in order to understand
134 the mechanism of presbyopia. This is also crucial when designing and evaluating
135 solutions for presbyopia, in particular the lens-based procedures.

136 Our study revealed the changing pattern of the lens inner components under
137 accommodation stimulation: the lens thickness increment mainly contributed to the
138 lenticular nucleus, but not the cortex. This is line with previous studies. However, the
139 change value in cortex and nucleus varied considerably among researchers due to use
140 of different techniques. Patnaik [6] firstly studied the component change during
141 accommodation using the slit-lamp photograph technique . He reported about 6
142 percent of lens changes in NT and only 0.5 percent of lens changes in the cortical
143 zones under -5~7D stimulation demand, but without the exact values reported. Later,
144 Brown [7] tested 5 cases and reported that the NT increased 0.07mm/D with -6D
145 accommodation stimulation in a 29 year old subject, while the posterior cortex
146 slightly increased. By using Scheimpflug slit-lamp photography, Koretz [8] found an
147 increase of 0.041mm/D for the NT, 0.002mm/D for the ACT, and 0.000mm/D for the
148 PCT under -2D accommodation stimulation. By deploying the Scheimpflug images
149 technique, with correction made for the distortion due to the geometry of the
150 Scheimpflug imaging system, Dubbelman et al [9] demonstrated an increase of 0.046
151 mm/D for the NT, only -0.001mm/D for the ACT, and -0.002mm/D for the PCT under
152 -6D accommodation stimulation. Later utilizing the same technique, they reported on
153 average 0.04 mm/D change for nucleus with accommodation in 5 young people [15].
154 In our study by using OCT, we only detected 0.03 mm/D for the NT under -6D

155 stimulation and both the ACT and PCT did not change significantly. In addition, those
156 differences could not only be from different techniques deployed, but other
157 contributors could also be age, race, and accommodation demand vs response. For
158 example, with the OCT, Martinez-Enriquez E [14] also tested the change in ALRC
159 and LT under accommodation stimulation. However, the change amplitude is different
160 to ours which were lower (ALRC -0.6mm/D vs -0.44 mm/D; LT 0.069 mm/D vs 0.03
161 mm/D).

162 Previous study showed that the nucleus becomes more convex in morphology
163 during accommodation [15]. In our study by using CASIA2 OCT to measure the
164 nucleus, the surface curvature and position were tested under different accommodative
165 stimulation states. We found that: the ANRC decreased much more than that of PNRC;
166 and the anterior nucleus surface moved forward significantly, but the posterior nucleus
167 surface did not move under accommodation. This indicated that the nucleus changed
168 non-uniformly under accommodative stimulation. We speculate that reasons for a non-
169 uniform change of the nucleus under accommodative stimulation are as following. The
170 human lens continues to grow throughout life, due to the addition of new lens fibers,
171 which gradually push away old fibers, which harden into the nucleus of the lens[16,
172 17]. While, Lens fibers from the anterior cortex are about 3 to 2.4 times greater than
173 those of the posterior cortex [9, 18], as a result, the anterior nucleus possibly less stiff
174 than the posterior nucleus could easily deform during accommodation. Second, the
175 asymmetry distribution of Zonular fibers (anterior, equatorial and posterior suspensory
176 ligament) between the anterior and posterior part of the lens [19], could result in

177 uniform stretching force and express in conformity mechanical changes when
178 accommodation induced ciliary muscle contraction [20]. In one word, these results
179 indicate that the lenticular nucleus plays a key role in accommodation. With age, the
180 crystal nucleus hardens and loses its response to accommodation and eventually causes
181 the development of presbyopia. Therefore, the lenticular nucleus should be the
182 primary target for accommodation restoration strategies of lens-based procedures for
183 presbyopia. Recently developed techniques such as lens photodisruption or component-
184 based lens refilling may be potential presbyopia correction techniques. It has been
185 reported that lens photodisruption with the femtosecond laser can improve lens
186 elasticity [1, 21-23] , but is limited by the ability to recover accommodation. In future,
187 the strategy could preferentially be to directly reduce the stiffness of the nucleus of the
188 older lens through refining laser patterns and pulse energies, which will achieve more
189 effectively accommodation restoration in presbyopia. Another technique is the
190 component-based lens refilling. The anterior curvature of the lens nucleus changes more
191 than the posterior part under accommodation. To reach similar morphological changes
192 under accommodation, the design strategy should somehow mimic the lens property
193 with gradient refractive index or material stiffness. Thus, possibly achieve phycological
194 re-construction of the lens and restore accommodation in presbyopia.

195 A major limitation of this study is that all included volunteers were healthy and
196 with a relatively narrow age range of 30-40 years. As accommodation ability usually
197 decreases with age, the changing pattern of the lens inner components under
198 accommodation with age needs to be further studied. Another limitation is that we

199 calculated lens components changes based on accommodative stimulus values, but not
200 subjective accommodative responses. The most accurate way would be to use
201 accommodative responses taken simultaneously with the image capture. The reason is
202 that those factors such as age, race, accommodation demand vs response could
203 contribute to variations in results.

204 In conclusion, when under accommodation stimulation, lens thickness changed
205 mainly due to the lenticular nucleus, but not the cortex. For the lenticular nucleus, the
206 ANRC decreased more than the PNRC and the nucleus became convex. Further, the
207 anterior surface of the nucleus moved forward while the posterior surface of the
208 nucleus moved backward but only slightly.

209 **METHODS:**


210 **Subjects:**

211 Twenty-three healthy adults from Tongji community were recruited and testing was
212 performed in Tongji hospital outpatient central. No subjects had any abnormal ocular
213 findings, or any history of ocular diseases, surgery, trauma, or contact lens. Subjects
214 were excluded when the best corrected visual acuity in each eye was lower than 20/20,
215 and the amplitude of accommodation less than -6D. This study was approved by the
216 research review board of Huazhong University of Science and Technology and the
217 study protocol registered with chictr.org.cn (ChiCTR-ROC-16008832). Informed
218 consent was obtained from each subject, and they were all treated in accordance with
219 the tenets of the Declaration of Helsinki.

220 **Experimental procedure:**

221 Serial regular ocular examinations were performed to screen subjects with ocular
222 diseases other than refractive error: these include slit lamp, fundus examination,
223 intraocular pressure (IOP) and subjective optometry. Afterwards, the amplitude of
224 accommodation was measured using the minus lens test as reported by León [24] and
225 subjects were excluded if their accommodation amplitude was less than -6D. Subjects
226 were then asked to undergo an OCT test in different accommodation stimuli.

227 **OCT image:**

228 OCT examination was performed under a standard procedure with a swept-source
229 OCT (CASIA2; Tomey Corporation, Nagoya, Japan) in the morning (9:00AM-
230 11:00AM). To avoid head movement between different scans, subjects were asked to
231 hold their jaw and forehead onto the fixed trestle, stare at the optotype with the testing
232 eye during scanning. The location of the machine was locked during testing. All OCT
233 images were obtained in the same examination room with controlled environmental
234 settings of temperature (15–25°C) and humidity (30–50%) and the light was dimmed
235 to avoid possible pupillary constriction. Before scanning, the refractive error was
236 corrected with a built-in program. Different accommodation states were achieved by a
237 built-in program and subjects were asked to clearly look forward at an internal fixation
238 target symbol “”. The lens analysis mode (Accommodation load, Starburst target.)
239 was used to capture images of the anterior segment of the eye. Pictures were taken when
240 the subject reported a clear view of the target symbol for 5 seconds at different
241 accommodation states in sequence organized as follows: 0D, -3D and -6D
242 accommodation stimuli.

243 **Image analysis:**

244 The CASIA2 enables some automatic measurements. Anterior segment parameter
245 measurements, including ATA, CT, ACD, ALRC and PLRC, were obtained from
246 images by the built-in software. The LT, ACT, PCT, NT, ANRC, PNRC, ANV and PNV
247 in each image were quantified manually and measured using the Image-pro plus
248 software (Version 6.0, MD, USA, <https://www.mediacy.com/>). Measuring items were
249 determined based on two-dimensional images (examples demonstrated in Fig1). The
250 anatomical details of the lens such as the capsule, cortex and nucleus can easily be
251 distinguished and identified (Figure 1A). The anterior and posterior interfaces of the
252 lenticular nucleus were segmented using edge detection with the tool of “Fit circle”.
253 The lenticular nucleus thickness (NT) defined in this study was equivalent to the
254 distance between the C3 zones base on the Oxford system [25, 26]. The ANRC and
255 PNRC were measured by manually depicting 3 points surrounding the outline of the
256 anterior and posterior surface of the nucleus. Then the ANRC and PNRC were
257 segmented and calculated utilizing this mi-automated fitting method with two elliptic
258 paraboloid surfaces using the best fit arc feature with the Image-pro plus software
259 (Figure 1B).

260 **Quality control:**

261 Researchers were trained before conducting the study. OCT scanning were
262 performed by a skilled operator. The scan was taken once for each accommodation
263 status and three times in total. The ambient lighting conditions were kept constant
264 during the whole procedure to avoid significant variations in pupil diameter. All

265 measurement items were sequentially measured under three different accommodation
266 conditions (0D, -3D, -6D accommodation). As we did before, the images of these eyes
267 were analyzed by two observers who were blinded to treatments, the intraobserver
268 reproducibility and interobserver reproducibility were also evaluated [27]. Only those
269 testing items whose intraclass correlation coefficient value is not less than 0.75 will be
270 presented.

271 **Statistical Analysis:**

272 Data were analyzed using SPSS 19.0 (IBM Corp., Armonk, NY, USA). The
273 sample size was calculated by assuming that there is a difference in lens thickness
274 between different accommodation states, for repeated measures analysis of variance
275 (rANOVA) with a correlation among repeated measures with a value of 0.8. A medial
276 level of partial eta square of 0.06 was adopted, which gave an effect size of about
277 0.25. A sample size of at least 19 participants was deemed to be sufficient to give us a
278 power of 0.80 with 95% confidence. The final sample size was adjusted to 23 based
279 on the 20% participant loss. Quantitative data are presented as mean \pm standard
280 deviation. Repeated measure ANOVA was performed to reveal significant differences
281 among different accommodation states. Prior to the repeated measure ANOVA, the
282 sphericity assumption was checked using the Mauchly's sphericity test. And when the
283 sphericity test was not statistically significant, the Greenhouse-Geisser correction was
284 applied. The Bonferroni procedure was used as a post hoc test for comparisons
285 between groups. $P < 0.05$ was set as statistical significance in all cases.

286

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353

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357 **Author contributions**

358 X.T, H.Z. and J.W contributed to the conception of the study; Y.X, F.T, Q.F, W.C.
359 Z.Q and J.M performed the experiment; C.D contributed significantly to analysis and
360 manuscript preparation; Y.X and A.M performed the data analyses and wrote the
361 manuscript; Y.X, P.W and H.Z helped perform the analysis with constructive
362 discussions

363

364 **Conflict of interest statement**

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

366 **Figure legend:**

367 Figure1.Examples of measured items and methods in CASIA2 optical coherence
368 tomography (OCT) image. A: Measured items: Anterior chamber depth (ACD), Lens
369 thickness (LT), Lenticular nucleus thickness(NT), Lenticular cortex thickness (CT),
370 Anterior cortex thickness (ACT), Posterior cortex thickness (PCT), Anterior lenticular
371 nucleus vertex (ANV), Posterior lenticular nucleus vertex (PNV). B: Showing
372 measurement methods for the anterior crystalline lens radius of the curvature (ALRC,
373 green) and the posterior crystalline lens radius of the curvature (PLRC, green). The
374 anterior crystalline lenticular nucleus radius of the curvature (ANRC, yellow arc), the
375 posterior crystalline lenticular nucleus radius of the curvature (PNRC, yellow arc).
376 (Note: Figure1 A rotated to show the optical axis vertically, figures were prepared by
377 Yan Xiang with Image-Pro Plus, Version 6.0, MD, USA, <https://www.mediacy.com>)

378

379 Figure2: The changes in the lens shape during accommodation. A: The changes of
380 lens thickness (LT) . B: The changes of anterior chamber depth (ACD). C: The
381 changes of anterior crystalline lens radius of curvature (ALRC). D: The changes of
382 posterior crystalline lens radius of curvature (PLRC). (compared with 0D, *P< 0.05,
383 **P< 0.01; compared with -3D, ## P< 0.01)

384

385 Figure3: The changes in lens components during accommodation. A: The changes of

386 lenticular nucleus thickness (NT), B: The changes of anterior cortex thickness (ACT),
387 C: The changes of posterior cortex thickness (PCT). (compared with 0D, **P< 0.01;
388 compared with -3D, ## P< 0.01)

389

390 Figure4. OCT images at different accommodative states in a 35-year-old male with -
391 1.5D myopia. A–C graphs show NT in different accommodation states; D–F graphs
392 show ANV and PNV in different accommodation states; H–G graphs show ALRC,
393 PLRC, ANRC and PNRC in different accommodation states. (Note: Figure 4 A-F
394 rotated to show the optical axis vertically, figures were prepared by Yan Xiang with
395 Image-Pro Plus, Version 6.0, MD, USA, <https://www.mediacy.com>)

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397

398 Figure5: The changes in the lenticular nucleus during accommodation. A: The
399 changes of anterior lenticular nucleus radius of the curvature (ANRC). B: The
400 changes of posterior lenticular nucleus radius of the curvature (PNRC). C: The
401 changes of anterior lenticular nucleus vertex (ANV). D: The changes of posterior
402 lenticular nucleus vertex (PNV). (compared with 0D, *P< 0.05, **P< 0.01; compared
403 with -3D, ## P< 0.01)

404