• Brief Report •

Post-miosis changes in the anterior chamber structures in primary and lens-induced secondary chronic angle-closure glaucoma

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Abstract

• To evaluate post-miosis changes in the anterior chamber structures in various angle-closure glaucomas (ACG). Totally 14 eyes of primary chronic angle-closure glaucoma (PCACG), 12 eyes of lens-induced secondary chronic angle-closure glaucoma (LSACG) and 14 healthy eyes were recruited. After miosis, for PCACG group, intraocular pressure (IOP) and anterior chamber depth (ACD) changed not significantly, while anterior chamber angle widened significantly. LSACG group showed a significant increase in IOP, decrease in ACD, and narrowing in anterior chamber angle. Healthy eyes showed significant decreases in IOP and anterior chamber parameters. Thus, miosis could widen the anterior chamber angle of patients with PCACG, while increase the narrowing of anterior chamber angle and IOP of patients with LSACG. We should pay attention to the distinction between PCACG and LSACG patients and the proper administration of pilocarpine in the treatment of patients with chronic ACG.

• **KEYWORDS:** miosis; chronic angle-closure glaucoma; anterior chamber structure; intraocular pressure; optical coherence tomography

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INTRODUCTION

Glaucoma was a leading cause of irreversible blindness worldwide[1-2], and could be categorized into two types: angle-closure glaucoma (ACG) and open angle glaucoma. In Asian, ACG is more prevalent than open angle glaucoma[3-5]. In terms of ACG, it could be divided into primary and secondary types. For the pathogenesis of primary ACG, besides the non-pupillary block mechanisms[6-11], the major mechanism was pupillary block[12-13]. As an initial option for primary ACG treatment, miotics could induce the contraction of the sphincter pupillae, which could then pull the peripheral iris away from the trabecular meshwork and therefore reopen the angle, and finally decrease intraocular pressure (IOP) and control the progression of glaucoma. For now, pilocarpine is still widely used in Asian due to the its inexpensiveness and effectiveness[14]. For the pathogenesis of secondary ACG, it would be different due to their different primary diseases. In terms of some secondary ACG, like secondary to zonular laxity and/or lens subluxation, the use of miotics may result in the further loosing of zonules and the forward movement of lens, causing the increase of pupillary block and the development of iris convex and angle closure[15-16]. The aim of this study was to evaluate the changes in anterior chamber structures in eyes with primary chronic angle-closure glaucoma (PCACG) and lens-induced secondary chronic angle-closure glaucoma (LSACG) after miosis using anterior segment optical coherence tomography (AS-OCT).

SUBJECTS AND METHODS

Ethical Approval The study was approved by the Ethics Committee of Tongji Hospital. All patients provided written informed consent ahead of participation. All study conduct adhered to the tenets of the Declaration of Helsinki.

Subjects Fourteen eyes from 14 patients with PCACG, twelve eyes from 12 patients with LSACG and fourteen eyes from 14 healthy subjects were recruited. Healthy subjects were included as negative control if 1) IOP of ≤21 mm Hg with no history of elevated IOP; 2) normal fundus, retinal nerve fiber thickness, visual field, and anterior chamber depth (ACD) with an open angle; 3) no family history of glaucoma. The chronic ACG was diagnosed based on 1) at least 180 degrees

of angle closure obliterating pigmented part of trabecular meshwork, whether synechial or appositional, segmented or continuous; 2) requiring IOP-lowering medications, or IOP >21 mm Hg without IOP-lowering medications; 3) visual field loss compatible with glaucoma and/or glaucomatous optic disc changes[17]. None of them had a history of acute glaucoma attacks or signs of acute glaucoma attack. All the patients underwent slit-lamp, gonioscopy, AS-OCT (Visante, USA) and ultrasound biomicroscopy (UBM; iUltrasound, USA) examinations to evaluate the status of zonules and anterior chamber structures. Patients who exhibited zonular dialysis, iridodonesis, anterior chamber angle closure, and shallower ACD in the affected eye in comparison with the fellow eye were defined as cases of LSACG[18]. And after excluding all other secondary chronic angle-closure glaucoma (SCACG) (*e.g.* secondary to iridocorneal endothelial syndrome, neovascular glaucoma, uveitis), the rest of chronic ACG was defined as PCACG. Study subjects were excluded if they had a history of eye disease (excluding ACG) or surgery, systemic disease or poor OCT image quality[19]. For healthy subjects, one eye was randomly selected. For PCACG patients, if both eyes of the patient were involved in glaucomatous damage, the more severe eye would be chosen as "affected eye"; if only one eye of the patient was involved, it would be "affected eye". For LSACG patients, the eye involved in glaucomatous damage was regarded as "affected eye". And all the affected eyes were selected to receive pilocarpine, to observe the post-miosis changes in the anterior chamber structures. Patients with pilocarpine treatment were required to withdraw of pilocarpine for two weeks before participation.

Pre- and Post-miosis IOP and AS-OCT Examinations IOPs were performed before miosis and every 5min after miosis (NIDEK RT-2100; Japan). If IOP was monitored to be constantly within 21 mm Hg after miosis, the subject would receive AS-OCT examinations 30min after miosis and the IOP value and OCT image at 30min after miosis would be regarded as the post-miosis IOP and OCT image. And if IOP was found >21 mm Hg after miosis, subject would receive AS-OCT examinations immediately instead of 30min post-miosis, and the IOP value and OCT image at this moment would be recorded as the post-miosis IOP and OCT image for further analysis. Moreover, the subject would also administrate oral methazolamide and be closely watched until the pupil and anterior chamber returned to pre-miosis level. AS-OCT were performed in the dark and the scan angle was horizontal across the center of the pupil. The operator adjusted the noise and optimized the polarization to ensure image quality.

Angle opening distance at 500 μm/750 μm from the scleral spur (AOD500/AOD750), trabecular-iris space area at 500 μm/750 μm from the scleral spur (TISA500/TISA750), ACD and pupil diameter (PD) were measured by the built-in software of the AS-OCT. The measurement methods were referred to the previous studies (Figure 1)[20-21].

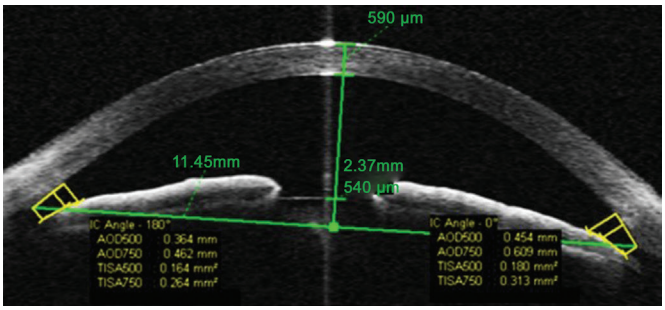

Figure 1 Schematic of ACD, angle opening distance 500 μm/750 μm from the scleral spur (AOD500/AOD750) and trabecular-iris space area at 500 μm/750 μm from the scleral spur (TISA500/TISA750) measurements.

Statistical Analysis All analyses were performed by SPSS 21.0. Comparison of demographic characteristics among three groups were performed by Kruskal-Wallis *H* test and Chi-square test. The general estimate equations were used to compare the AOD500/750 and TISA500/750 before and after miosis, and the paired sample *t*-test was used to compare ACD between two eyes of one subject, and to compare IOP, ACD and PD before and after miosis. All tests were two-tailed, and statistical significance was defined as a P value of <0.05.

RESULTS

Subjects Characteristics The demographic data are shown in Table 1. There were no significant differences in age, sex, and central corneal thickness (CCT) among three groups. Axial length (AL) was significantly shorter, refractive error (RE) and IOP were significantly higher in PCACG group compared with LSACG and healthy groups.

ACD of Affected Eyes and Fellow Eyes in PCACG, LSACG and Healthy Groups Compared with fellow eyes, ACDs of the affected eyes were significantly shallower in both PCACG and LSACG groups, while no such significant difference was found in healthy group (Table 2). The difference between ACD value of fellow eyes and ACD value of affected eyes (ΔACD) were significant larger in PCACG and LSACG groups compared with healthy group. In terms of glaucomatous groups, no significant ΔACD difference between PCACG and LSACG groups was found (Table 3).

Comparison of AOD500/750, TISA500/750, ACD, PD and IOP of Affected Eyes Before and After Miosis in PCACG, LSACG and Healthy Groups Post-miosis ACD and IOP showed no significant changes, while post-miosis AOD500/750 and TISA500/750 increased significantly in PCACG group. Conversely, in terms of anterior chamber structure of LSACG and healthy groups, post-miosis AOD500/750, TISA500/750 and ACD decreased significantly. However, in terms of IOP,

Table 1 Demographic characteristics comparison among PCACG, LSACG and healthy groups

Parameters	PCACG	LSACG	Healthy subject	P^a	P^b	P^c
Age (y)	43.1±8.2	38.3±6.1	38.9±8.6	0.128	0.152	0.975
Male (%)	42.86	41.67	50.00	0.951	0.705	0.671
CCT (μm)	542.5±24.2	533.3±24.4	537.1±30.4	0.262	0.878	0.330
AL (mm)	21.71±0.50	22.95±1.09	23.64±0.81	0.003[c]	<0.001[d]	0.149
RE (D)	0.18±0.85	-0.97±1.71	-1.23±1.13	0.036[c]	0.003[d]	0.427
IOP (mm Hg)	18.57±1.68	16.16±1.54	16.31±1.65	0.002[c]	0.003[d]	0.767

[a]*P* value between PCACG and LSACG; [b]*P* value between PCACG and healthy group; [c]*P* value between LSACG and healthy group. [d]Significance of difference: Kruskal-Wallis *H* test.

Table 2 Comparison of ACD between affected eyes and fellow eyes in PCACG, LSACG and healthy groups

ACD (mm)	Affected (selected) eyes	Fellow (non-selected) eyes	*P*
PCACG	2.00±0.25	2.13±0.20	0.007[a]
LSACG	2.39±0.20	2.59±0.23	<0.001[a]
Healthy subjects	3.11±0.38	3.14±0.39	0.169

[a]Significance of difference: paired *t*-test.

Table 3 Comparison of difference between ACD value of fellow eyes and ACD value of affected eyes (ΔACD) among PCACG, LSACG and healthy groups

Parameters	PCACG	LSACG	Healthy subject	P^a	P^b	P^c
ΔACD (mm)	0.14±0.16	0.20±0.11	0.03±0.08	0.206	0.045[d]	0.001[d]

ΔACD: The difference between ACD value of fellow eyes and ACD value of affected eyes. [a]*P* value between PCACG and LSACG; [b]*P* value between PCACG and healthy group; [c]*P* value between LSACG and healthy group. [d]Significance of difference: Kruskal-Wallis *H* test.

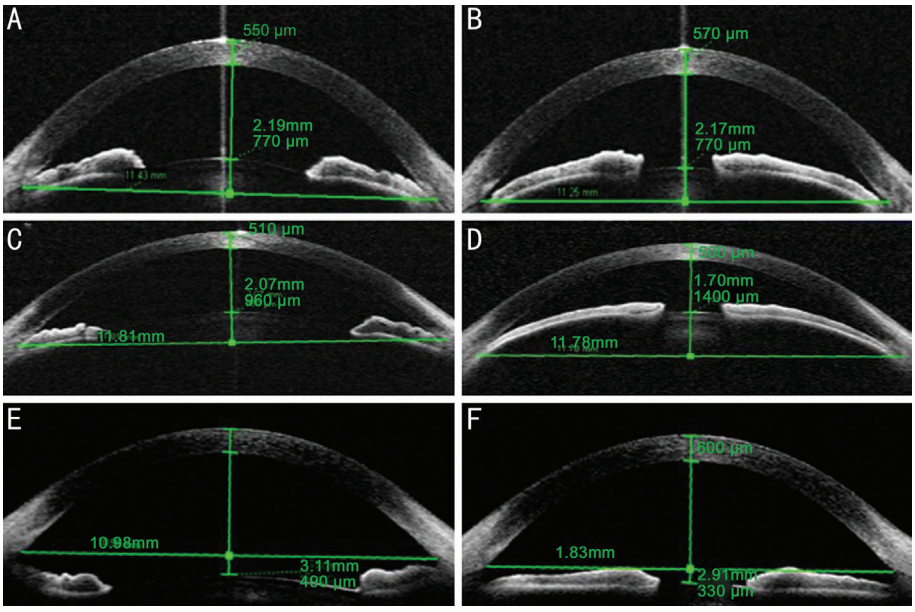

Figure 2 Changes in the anterior chamber after miosis The ACD of the eye with PCACG stayed relatively unchanged and the anterior chamber angle became wider after miosis (A, B). In contrast, the ACD decreased significantly by 0.37 mm in the eye with LSACG after miosis, and the anterior chamber angle also became narrower (C, D). For healthy eyes, after miosis, the ACD decreased significantly and the anterior chamber angle became less wide (E, F).

the change trends of LSACG and healthy groups were opposite to each other: LSACG group had a significant post-miosis increase in IOP, while healthy group had a significant post-miosis decrease in IOP (Table 4; Figure 2).

DISCUSSION

As a miotic, besides its effect on the pupil, the administration of pilocarpine could also induce the contraction of the ciliary muscle, then the relaxation of zonule and changes in the

Table 4 Comparison of AOD500/750, TISA500/750, ACD, PD and IOP of affected eyes before and after miosis in PCACG, LSACG and healthy groups

Parameters	Before miosis	After miosis	*P*
PCACG			
AOD500 (mm)	0.111±0.064	0.167±0.093	0.003[a]
AOD750 (mm)	0.161±0.063	0.215±0.092	0.001[a]
TISA500 (mm^2)	0.053±0.029	0.072±0.043	0.001[a]
TISA750 (mm^2)	0.089±0.040	0.122±0.062	<0.001[a]
ACD (mm)	2.00±0.24	2.02±0.22	0.091
PD (mm)	4.77±0.47	2.20±0.61	<0.001[b]
IOP (mm Hg)	18.57±1.68	17.95±1.38	0.243
LSACG			
AOD500 (mm)	0.155±0.102	0.117±0.066	0.006[a]
AOD750 (mm)	0.225±0.126	0.188±0.085	0.004[a]
TISA500 (mm^2)	0.060±0.045	0.044±0.029	0.009[a]
TISA750 (mm^2)	0.107±0.070	0.080±0.043	0.005[a]
ACD (mm)	2.39±0.22	2.17±0.36	0.002[b]
PD (mm)	5.04±0.75	2.03±0.30	<0.001[b]
IOP (mm Hg)	16.16±1.54	18.15±2.59	0.001[b]
Healthy subject			
AOD500 (mm)	0.713±0.345	0.554±0.182	0.012[a]
AOD750 (mm)	0.953±0.411	0.716±0.209	0.001[a]
TISA500 (mm^2)	0.259±0.137	0.212±0.070	0.048[a]
TISA750 (mm^2)	0.462±0.216	0.365±0.127	0.006[a]
ACD (mm)	3.11±0.38	2.89±0.36	<0.001[b]
PD (mm)	5.18±0.98	1.93±0.44	<0.001[b]
IOP (mm Hg)	16.31±1.65	14.81±1.93	<0.001[b]

[a]Significance of difference: General estimate equations; [b]Significance of difference: Paired *t*-test. AOD500/AOD750: Angle opening distance at 500 μm/750 μm from the scleral spur; TISA500/TISA750: Trabecular-iris space area at 500 μm/750 μm from the scleral spur.

lens shape, resulting in the increase in the lens thickness and anterior surface curve[22]. Given that ACD was measured as the length of central perpendicular line between posterior surface of the cornea and anterior surface of the lens[21], the increase in lens thickness and anterior surface curve could cause the observed decrease in ACD. And the increase in the lens thickness and anterior surface curve could also pull the iris anteriorly to the cornea, making the anterior chamber angle less wide. In addition, although the anterior chamber of healthy subject became shallower after miosis, post-miosis IOP of healthy subject showed a significant decrease. The reason for that could be the effect of miotic on the conventional aqueous humor outflow pathway. Even if the normal anterior chamber angle became less wide after miosis, however, it still remained open, ensuring the normal aqueous humor drainage. Additionally, the contraction of ciliary muscle induced by pilocarpine could also stretch the trabecular meshwork and Schlemm's canal *via* scleral spur and connecting fibrils between ciliary body and Schlemm's canal, and then increase the aqueous humor outflow facility and decrease in IOP[23-25]. For PCACG group, the post-miosis changes in anterior chamber structure was opposite to healthy subjects, showing a wider anterior chamber angle. For LSACG group, although its change trend of anterior chamber structure was similar to healthy subjects (shallower anterior chamber and narrower anterior chamber angle after miosis), its change trend of IOP was completely contrary to healthy subject (post-miosis IOP of LSACG showed a significant increase while that of healthy subject showed a significant decrease). Thus, the post-miosis changes in PCACG and LSACG groups were different from healthy subject, indicating that the post-miosis changes in these two glaucomatous groups were not physiological but pathological, and those pathological changes could be relevant to the disease of ACG itself.

After the administration of pilocarpine, PCACG and LSACG groups showed a distinct change trend in anterior chamber structures. For PCACG patients, post-miosis anterior chamber angle widened significantly. Miosis could decrease or eliminate the pupillary block, pull the peripheral iris away from the trabecular meshwork, and finally open the anterior chamber angle[14,26]. In addition, although the anterior chamber angle widened after miosis, IOP only showed a non-significant decrease. In this study, our subjects were chronic glaucomatous patients. The long chronic disease course might have partly or totally damaged the aqueous humor outflow pathway and disabled the drainage ability of the affected eyes. Thus, even though miosis could open or widen the anterior chamber, the aqueous humor would still not fluently drainage through the damaged outflow pathway, resulting in the non-significant change in IOP after miosis. For LSACG group, pilocarpine showed a contrary effect with narrowing in the anterior chamber angle, shallowing in ACD and elevation in IOP. The mechanism might be the zonule. The zonular apparatus is the main support system of the lens. Weakened zonules allow the lens to be mobile and move anteriorly. This could result in the forward lens movement, a shallower anterior chamber, increased pupillary block and iris convexity[27-29], which increase the risk for an angle-closure event[29-30]. All the LSACG patients in this study showed certain evidences of zonule laxity, thus, the administration of pilocarpine would contract the ciliary muscle and further loose the zonule, leading to further displacement of lens, the exacerbation of pupillary block and forward movement of lens-iris diagram and finally the narrowing of anterior chamber angle and increase in IOP. Although both PCACG and LSACG showed signs of chronic ACG, their responses to miotics were different. Thus, we should pay more attention to the chronic ACG patients

with suspect of secondary to zonular laxity and avoided the improper administration of pilocarpine on them, which would close the anterior chamber angle and elevate IOP further.

Our results suggested that the ACD difference between affected and fellow eyes in LSACG group was similar to that in PCACG group. For LSACG patients, the displacement of lens and its influence on the anterior chamber were not obvious, and there might also be no other significant signs (*e.g.* serious eye pain or headache, irisopsia) of elevated IOP. Combined with its chronic disease course, it could be very likely to misdiagnose LSACG as PCACG. Therefore, a detailed history taking, a slit-lamp examination, a necessary AS-OCT or UBM examination to evaluate the status of zonule were important for the distinction between PCACG and LSACG and also meaningful for the correct treatment selection.

In conclusion, we should pay attention to the distinction between PCACG and LSACG patients and the proper administration of pilocarpine in the treatment of patients with chronic ACG.

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