·Clinical Research·

Anterior segment changes after pharmacologic mydriasis using Pentacam and optical coherence tomography in angle closure suspects

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Abstract

• AIM: To compare the dynamic changes of anterior segment parameters especially iris morphology induced by pharmacologic mydriasis between angle closure suspects and normal controls.

• METHODS: The study group comprised 19 eyes of 19 angle closure suspects and 19 eyes of 19 age- and sex-matched normal open-angle eyes. Pentacam and optical coherence tomography measurements before and 30min after instillation of compound tropicamide eye drop were performed and compared. Biometric evaluations of iris tomography and anterior chamber angle were estimated by a customized image-processing software.

• RESULTS: Baseline axial length, iris cross sectional area and volume did not differ significantly between angle closure suspects and normal controls. Angle closure suspects had smaller pupil size, narrower anterior segment dimension and axial length, thinner iris with greater curve in comparison with normal controls. Pharmacologic mydriasis led to significant increments in iris thickness at 750 μm, anterior chamber depth and volume, whereas significant decrements in iris curve, cross sectional area and volume in both groups. Angle opening distance at 500 μm was increased significantly in normal controls (from 0.465±0.115 mm to 0.539±0.167 mm, P=0.009), but not in angle closure suspects (from 0.125±0.100 mm to 0.145±0.131 mm, P=0.326). Iris volume change per millimeter of pupil dilation (△IV/△PD) decreased significantly less in angle closure suspects than normal controls (-2.47±1.33 mm² *vs* -3.63±1.58 mm², P=0.019). Linear regression analysis showed that the change of angle opening distance at 500 μm was associated most with the change of central anterior chamber depth (β=0.841, P=0.002) and △IV/△PD (β=0.028, P=0.002), followed by gender (β=0. 062, P=0.032).

• CONCLUSION: Smaller iris volume decrement per millimeter of pupil dilation is related significantly with the less anterior angle opening in angle closure suspects after pharmacologic mydriasis. Dynamic iris change may be as a prospective indicator of iris compressibility and angle closure glaucoma.

• KEYWORDS: pharmacologic mydriasis; primary angle closure suspects; anterior segment change; iris volume

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INTRODUCTION

Primary angle closure glaucoma (PACG) is associated with a second leading cause of blind and a major public health concern worldwide. According to Quigley and Broman [1], by 2020, over 10 million people will have PACG in China, containing the greatest number in the world. People with angle closure disease may suffer from primary angle closure suspect (PACS), primary angle closure (PAC) and PACG. PACS has always been defined as an angle in which more than 270° of the posterior trabecular meshwork cannot be seen [2]. However, the majority of such eyes never develop PAC or PACG in epidemiological researches [3-5]. To know which eye has high risk for PAC or PACG is mandatory to be able to select right people from large number of PACS for preventive treatment. However, the mechanism of PACS to PAC and PACG is intricate and still vague.

Anterior chamber angle is dynamic under different physiological conditions. Previous studies of provocative tests have shown that increased pupillary block and angle closure might occur during physiological or pharmacological pupil dilation[6-9]. However, some investigations have elucidated that angle narrowing also could develop while peripheral iridectomy eliminates pupillary block [10-12]. There is likely an interplay of dynamic ocular structures that increases the risk of angle closure with the exception of pupillary block

mechanism. Documenting those changes of ocular biological parameters may be important as it has implications as to find which dynamic configuration effects the pathogenesis of angle closure most. Recent anterior segment imaging techniques such as optical coherence tomography (OCT) and Pentacam have allowed us to obtain quantitative and objective data of various dynamic changes probably.

The purpose of our study was to evaluate the dynamic changes of anterior segment parameters during pharmacologic mydriasis between PACS and normal eyes. The results may provide insights into the dynamic mechanism of narrow-angle development as well as helpful information for ophthalmologists in clinical prevention and treatment of angle closure disease.

SUBJECTS AND METHODS

Subjects This prospective comparative study was approved by the Department of Ophthalmology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, and adhered to the Declaration of Helsinki. All subjects were Chinese Han nationality, and provided written informed consents.

All enrolled PACS were according to the following criteria: 1) the invisibility of posterior trabecular meshwork (>270°) under static gonioscopy; 2) the absences of peripheral anterior synechiae and glaucomatous optic neuropathy; 3) intraocular pressure (IOP) of 21 mm Hg or less[2]. In addition, all the PACS were complicated with mild cataracts and required surgeries of phacoemulsification. During the preoperative preparations for phacoemulsification, pharmacologic mydriasis was performed and compared.

All the control subjects were recruited from outpatient service for mydriatic fundus examination, who had open angles with grade 3-4 angle depths in the Shaffer classification.

The exclusion criteria included: 1) corneal or conjunctival abnormalities that precluded image quality; 2) any use of medications which might affect the iris and angle configuration such as norepinephrine, cholinergics and adrenergic agonists or antagonists; 3) hypertension, cardiac-cerebral vascular disease, and diabetes mellitus; 4) histories of intraocular surgery and trauma; 5) refractive error (spherical equivalent less than -3.00 D or greater than +3.00 D); 6) eye with plateau iris.

Examination and Image Analysis All the enrolled eyes underwent a thorough ophthalmological examination, including objective and subjective refraction, IOP measurement by Nidek-NT2000 (Nidek Co. Ltd., Gamagori City, Japan), slit-lamp examination and fundus examination with direct ophthalmoscope (66 Vision Tech Co., Ltd., Jiangsu Province, China). They also underwent an axial length(AL) examination with IOL Master(Carl Zeiss Meditec AG, Jena, Germany), a retinal nerve fibre layer measurement with Stratus OCT version 4.0.5 (Carl Zeiss Meditec Inc., Dublin, CA, USA) and a 30-2 threshold protocol of visual field analysis with Humphrey Visual Field Analyzer II (Carl Zeiss Meditec Inc., Dublin, CA, USA). Gonioscopy with 4 mirror lens (66 Vision Tech Co., Ltd., Jiangsu Province, China) was performed by an independent ophthalmologist who was masked to the results of this study.

Pentacam and OCT imaging were performed in a dark room (<1 lx) after 30s of dark adaptation. Anterior segment parameters of central anterior chamber depth (CACD), anterior chamber volume (ACV), central corneal thickness (CCT), corneal volume (CV), corneal keratometry (Km) and astigmatism(Astig) were obtained automatically by pentacam scheimpflug system (Pentacam; Oculus Gmbh, Wetzlar, HE, Germany) with the quality score >95. The Pentacam could obtain 25 images of anterior segment in 2s to rebuild a three-dimensional image using a monochromatic blue light (475 nm) and a rotating scheimpflug camera. Peripheral anterior chamber depth (PACD) was calculated by averaging the values of anterior chamber depth at eight meridians and 4 mm distance from the corneal centre.

Then OCT (Visante,Carl Zeiss Meditec Inc., Dublin, CA, USA) examinations were performed with an enhanced anterior segment single protocol. The scan line was manually adjusted to the pupil. All eight quadrants (0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°) were obtained after clear visualizations of scleral spur and center corneal reflection. A customized image-processing software (MatLab 7.10.0.499 R2010a; The MathWorks, Natick, MA, USA) was used for image analysis. The definitions of anterior segment parameters have been described in detail elsewhere: 1) pupil diameter (PD) was calculated as the distance between the pupil margins; 2) angle opening distance at 500 μm (AOD500) was calculated as the distance from the corneal endothelium to the iris surface perpendicular to a line drawn at 500 μm from the scleral spur; 3) iris thickness was measured at 750 μm (IT750) and 2000 μm (IT2000) anterior to the scleral spur as the shortest distance between the anterior and posterior iris surfaces; 4) iris curvature (I-curv) was determined by creating a line from the most peripheral to the pupillary edge and then measuring the perpendicular distance from this line to the greatest convexity point along posterior iris surface; 5) iris cross-sectional area (IS) was calculated as the cumulative cross sectional area of the full length (from spur to pupil) of the iris [13]. An average of 4 cross-sectional parameters was calculated for each eye. The iris volume (IV) could be estimated according to the Pappus-Guldin centroid theorem as described previously[14].

All these images were acquired and evaluated in the same environment 30min after instillation of one drop of

compound tropicamide (0.5% phenylephrine and 0.5% tropicamide; Sinqi Pharmaceutical Co., Ltd., Shenyang, Liaoning Province, China) by the same observer. IOP was measured three times at ten-minute intervals to ensure that it was less than 30 mm Hg.

Statistical Analysis SPSS statistical software version19.0 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. The one-sample Kolmogorov-Smirnov test was used to assess the normality of the parameter evaluations. The Fisher's exact probability was used for the analysis of dichotomous variables. Comparisons of parameters between PACS and normal controls were performed with the independent *t*-test. The Pairwise *t*-test was conducted to calculate differences before and after mydriasis. The Pearson analysis was performed to evaluate the relationships between the change in AOD500 and age, gender, diagnosis, baseline parameters and other anterior segment changes. Variables that were significant at a level of $P<0.05$ were included in a stepwise regression model.

RESULTS

We studied 19 PACS eyes of 19 patients recruited from March 2014 to August 2014, and 19 eyes of 19 age- and sex-matched normal open-angle eyes. The mean ages of PACS and normal controls were 59.5±11.2y and 54.5±11.9y respectively. PACS had smaller AL, shallower anterior chamber (CACD, PACD, ACV, AOD500), thinner IT750, greater I-curv, and smaller PD compared with parameters of normal controls (P <0.05). There were no significant differences in IS, IT2000, IV, and corneal parameters between these two groups. The baseline demographic and biometric characteristics of study participants were summarized in Table 1.

Thirty minutes after instillation of compound tropicamide eye drop, AOD500 did not change significantly in the PACS (△AOD500=-0.020±0.087 mm; P=0.326), whereas it increased in the normal controls (△AOD500=-0.074±0.111 mm; P=0.009). The change in IV with pupil dilation differed between the two groups. Mean IV change per millimeter of pupil dilation (△IV/△PD) was -3.63±1.58 mm^2 in the normal controls, while -2.47±1.33 mm^2 in the PACS (P=0.019). Other anterior chamber changes were similar in both groups. Table 2 presented the comparison of anterior segment changes before and after pharmacologic mydriasis.

The results of Pearson analysis and regression regression of △AOD500 were shown in Table 3. Gender, baseline I-curv, CACD, PACD, ACV and △IV/△PD, △CACD, △PACD were related significantly with △AOD500 in both groups. Furthermore, the stepwise analysis showed that the variables associated significantly with △AOD500 were △CACD and △IV/△PD, followed by gender.

Table 1 The baseline demographic and biometric characteristics

Parameters	Normal controls	PACS	*P*
Age (a)	54.5±11.9	59.5±11.2	0.195
Gender (M/F)	4/15	8/11	0.495
Eye (right/left)	9/10	9/10	1.000
AL (mm)	23.21±1.10	22.60±0.61	0.042
PD (mm)	4.418±0. 851	3.466±0.798	0.001
I-curv (mm)	0.237±0.056	0.340±0.066	<0.001
IT750 (mm)	0.473±0.037	0.444±0.072	0.129
IT2000 (mm)	0.560±0.043	0.449±0.054	<0.001
IS (mm^2)	1.685±0.139	1.804±0.227	0.060
IV (mm^3)	43.13±2.60	43.33±5.77	0. 893
AOD500 (mm)	0.465±0.115	0.125±0.100	<0.001
CACD (mm)	2.54±0.28	1.93±0.19	<0.001
PACD (mm)	1.94±0.30	1.34±0.18	<0.001
ACV (mm^3)	120.8±27.2	72.9±15.3	<0.001
CCT (μm)	550.7±32.1	533.9±27.7	0.092
CV (mm^3)	61.5±3.7	59.7±3.7	0.123
Km/front (D)	44.1±1.6	44.0±1. 7	0. 846
Km/back (D)	-6.5±0.2	-6.5±0.2	0. 889
Astig/front (D)	0.95±0.72	0.87±0.67	0.746
Astig/back (D)	0.26±0.11	0.30±0.10	0.279

PACS: Primary angle closure suspects; AL: Axial length; PD: Pupil diameter; I-curv: Iris curvature; IT750/IT2000: Iris thickness at 750 μm/ 2000 μm; IS: Iris cross sectional area; IV: Iris volume; AOD500: Angle opening distance at 500 μm; CACD: Central anterior chamber depth; PACD: Peripheral anterior chamber depth; ACV: Anterior chamber volume; CCT: Central corneal thickness; CV: Central corneal volume; Km: Corneal keratometry; Astig: Corneal astigmatism. Values are given as mean±SD. *P*: Compare between normal controls and PACS. *P* is significant when <0.05.

DISCUSSION

It has long been known that physiological or pharmacological mydriasis is associated with the rise of intraocular pressure and the processes of angle closure glaucoma [6-9]. With the development of new devices for assessment of anterior chamber such as OCT, ultrasound biomicroscopy, and pentacam, dynamic features of normal characteristic and mechanism of disease states such as angle closure attack are now within reach.

Recent studies have demonstrated that some anterior chamber structures may be involved in the angle closure risk during physiologic or pharmacologic pupil dilation. Of the reported studies, Hirose *et al* [15] elucidated an association between iris thickness difference and AOD500 difference form light to dark conditions in the angle closure subjects and open angles, their research found that thickening of the iris root under dark conditions was related to the angle closure. Cheung *et al* [16] examined the dynamic responses of iris configuration using OCT, and found all the narrow angles had convex-to-convex iris anatomy in dark and light conditions, while half of the open angles showed this pattern. They hypothesized that as iris configuration might reflect the pressure differential across the iris, the potential dynamic iris bowing as the pupil change might predispose some small

Table 2 Comparison of anterior segment changes before and after pharmacologic mydriasis

Parameters	Normal controls		PACS		P^2
	Mean±SD	P^1	Mean±SD	P^1	
△I-curv (mm)	0.113±0.050	<0.001	0.146±0.191	0.004	0.474
△IT750 (mm)	-0.096±0.034	<0.001	-0.093±0.042	<0.001	0.772
△IS (mm^2)	0.523 ±0.162	<0.001	0.544 ±0.167	<0.001	0.694
△IV (mm^3)	8.758±3.242	<0.001	7.212±3.654	<0.001	0.176
△AOD500 (mm)	-0.074±0.111	0.009	-0.020±0.087	0.326	0.106
△CACD (mm)	-0.098±0.055	<0.001	-0.069±0.042	< 0.001	0.077
△PACD(mm)	-0.612±0.116	<0.001	-0.569±0.111	<0.001	0.254
△ACV (mm^3)	-20.00±9.4	<0.001	-24.74±10.69	<0.001	0.157
△CCT (μm)	-5.05±7.69	0.010	-2.53±9.18	0.246	0.364
△CV (mm^3)	-0.600±1.239	0.049	-0.279±1.181	0.317	0.419
△IV/△PD (mm^2)	-3.63±1.58	-	-2.47±1.33	-	0.019

PACS: Primary angle closure suspects; △I-curv: Iris curvature changes; △IT750: Iris thickness changes at 750 μm; △IS: Iris cross-sectional area changes; △IV: Iris volume changes; △AOD500: Angle opening distance changes at 500μm; △CACD: Central anterior chamber depth changes; △PACD: Peripheral anterior chamber depth changes; △ACV: Anterior chamber volume changes; △CCT: Central corneal thicknes changes; △CV: Central corneal volume changes; △PD: Pupil diameter changes; △IV/△PD: Mean iris volume change per millimeter of pupil dilation. P^1: Compare between before mydriatic and after mydriatic; P^2: Compare between normal controls and PACS. P is significant when <0.05.

Table 3 Person analysis and stepwise regression for △AOD500

Parameters	Person analysis		Stepwise regression	
	β	P	β	P
Gender	-0.339	0.037	-0.062	0.032
I-curv (mm)	0.357	0.028	-	-
CACD (mm)	-0.453	0.004	-	-
PACD (mm)	-0.380	0.018	-	-
ACV (mm^3)	-0.435	0.006	-	-
△IV/△PD (mm^2)	0.405	0.012	0.028	0.002
△CACD (mm)	0.495	0.002	0. 841	0.002
△PACD (mm)	0.404	0.012	-	-

△AOD500: Angle opening distance changes at 500 μm; I-curv: Iris curvature; CACD: Central anterior chamber depth; PACD: Peripheral anterior chamber depth; ACV: Anterior chamber volume; △IV/△PD: Mean iris volume change per millimeter of pupil dilation; △CACD: Central anterior chamber depth changes; △PACD: Peripheral anterior chamber depth changes; β: Standardized coefficients. Stepwise regression: R=0.690; R^2=0.476; P=0.000. P is significant when < 0.05.

eyes to angle closure. Similarly, another study found that the iris of angle closure eyes stretched less and developed a more convex configuration in response to illumination, which might be as a result of increased relative pupillary block[17]. In contrast to the above studies, we showed that pharmacologic mydriasis leaded to a similar increment in iris thickness, whereas a similar decrement in iris I-cure in both groups[9]. Moreover, some investigations found that angle closure and IOP increment also could happened while the peripheral iridectomy eliminates pupillary block [10-12]. It was currently believed that the angle closure during mydriasis did not only contribute to the iris convex and the pupillary block, but also some other iris inherent property.

The development of angle closure has been thought to represent a complicated multi-factor mechanism. Several authors have documented that iris volumetric compression less leaded to angle closure more after physiological or pharmacological mydriasis. Quigley *et al* [18] found that angle closure patients had smaller iris cross-sectional area changes in response to pupil dilation than did open angle glaucoma, and smaller iris cross-sectional area changes with physiologic pupil dilation indicating that the dynamic response of iris volumetric property might contribute to angle closure in addition to static characteristics. Aptel *et al* [19] demonstrated directly, using a geometrical method, IV increased in the fellow eyes of acute angle closure, whereas it decreased significantly in the open-angle eyes after pupil dilation. Furthermore, in another study, they estimated IV in the fellow eyes of angle closure patients as well as PACS eyes and normal open-angle eyes, and found that IV increased in all the fellow eyes, whereas it decreased significantly in most PACS eye, and in all open-angle eyes[20]. In a similar manner, Ganeshrao *et al* [21] found a less decrement of IV in angle closure eyes compared with the normal Indian. In agreement with those studies, we showed that IV changes in response to pharmacological mydriasis differed significantly between the angle closure suspects and normal controls in Chinese adults. Regression analysis certified △ACD and △IV/△PD were the major determinants of angle width change and the risk of angle closure.

In addition, further study improved the stromal transmissibility, especially extracellular fluid transfer, vascular tonus disturbance, or both with pupil block increment might influenced the physiologic compressibility of iris [22-24]. Those difference was advanced to explain the volumetric response of iris which was similar to the characteristics of sponge. It was reasonable for us to assume

that the iris compressibility might play a protective role in avoiding the angle closured during mydriasis.

There were several limitations of this work. This study used a combined preparation of α1-adrenergic receptor agonist and an anti-muscarinic drug. In further work, it would be interesting to perform similar investigations after physiologic pupil dilation. Baseline iris parameters and pupil size should be taken into account in any analysis of angle and iris structures changes. In our study, baseline pupil size in the darkness was significantly smaller in the PACS than the open-angle eyes. In the dark, the degree to which a pupil dilates could be regarded as predominantly a measure of sympathetic function [25]. Brazier [26] once found resting darkness PD was reduced in acute PACG (APACG) when compared to open angle eyes. Its correlation with ACD implies that iris autonomic function was reduced in eyes with shallow anterior chambers. The relationship between pupil response and PACS need for further research. It is ethically impossible to perform pupil dilation in the narrow angle eyes without a prophylactic iridotomy. But iridotomy may change the dynamic response of the iris during pupil dilation. The number of PACS in our study is not much, all the PACS in our study associated with mild cataract and decided to do the phacoemulsification. During the preoperative preparation of pharmacologic mydriasis we did the study and obtained informed consent. None of them had acute angle closed and intraocular pressure above 10 mm Hg measured 30min after instillation of compound tropicamide.

In summary, a less IV decrease after pupil dilation was associated significantly with a greater angle narrowing(larger relative AOD500) in these narrow-angle eyes. Therefore, it can be speculated that this dynamic behavior of the iris is one of the mechanisms involved in the development of angle closure during mydriasis.

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