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Effect of topical application of adrenaline on Schlemm canal, trabecular meshwork and intraocular pressure

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Abstract

Aim: To measure changes in the sizes of Schlemm canal (SC) and trabecular meshwork (TM) in healthy individuals before and after topical application of 1% adrenaline at 15, 45, and 90 minutes using anterior segment optical coherence tomography (ASOCT).

Methods: Anterior chamber angle imaging of the nasal and temporal regions of the right eyes was performed with anterior segment optical coherence tomography (ASOCT) before and after topical application of 1% adrenaline at 15, 45, and 90 minutes. The diameter and area of SC, width and thickness of TM, anterior chamber depth (ACD) and pupil diameter (PD) were measured with ASOCT images. Intraocular pressure (IOP) was also recorded simultaneously.

Results: A total of 15 healthy individuals were enrolled and included 7 male subjects and 8 female subjects; Compared with the parameters before intervention, both the SC diameter and area in the 2 quadrants increased after the application of adrenaline at the 3 time points ($P < .05$). The TM width increased after medication ($P < .05$). IOP decreased significantly after application ($P < .05$). There were no statistically significant changes in TM thickness, ACD, and PD at any point of time ($P > .05$).

Conclusion: Topical application of 1% adrenaline in eye led to decrease in IOP with the SC diameter and area as well as the TM width increased after medication. While the TM thickness, ACD, PD seemed to remain constant.

Abbreviations: ACD = anterior chamber depth, AL = axial length, ASOCT = anterior segment optical coherence tomography, BCVA = best-corrected visual acuity, CCT = central corneal thickness, IOP = intraocular pressure, JCT = juxtacanalicular tissue, LC = locus coeruleus, OCT = optical coherence tomography, PD = pupil diameter, POAG = primary open angle glaucoma, SC = Schlemm canal, SS = scleral spur, TM = trabecular meshwork, WDT = water-drinking test.

Keywords: adrenaline, healthy individuals, optical coherence tomography, Schlemm canal, trabecular meshwork

1. Introduction

Glaucoma is the mean cause of irreversible blindness worldwide, which is characterized by atrophy of the optic nerve and loss of field vision.[1] Elevated IOP, advanced age and genetics are considered to be the main risk factors for disease onset. Current treatments for glaucoma involve lowering IOP including laser trabeculoplasty, glaucoma filtration surgery and antiglaucoma medications,[2] and neuroprotective therapies such as neurotrophic factors and some traditional Chinese medicine.[3] The major risk factor for the axonal loss in glaucoma is the pathological elevation of the IOP, thus lowering IOP is the primary proven effective therapeutic strategy at present. IOP is determined by the balance of aqueous humor production and outflow. The aqueous humor is secreted by the ciliary body and then arrives in anterior chamber, flowing through trabecular meshwork (TM) and draining into Schlemm canal (SC), eventually reaching the episcleral venous circulation. It was recognized that the major aqueous outflow resistance located in the juxtacanalicular tissue (JCT) region and the inner wall of SC.[4]

Previous studies have shown that the status of SC and TM was closely related to the level of IOP.[5–7] Our prior study indicated that patients with primary open angle glaucoma (POAG) had morphological abnormalities in structure of SC and TM, representing smaller canal diameter of SC and reduced thickness of TM compared with normal individuals.[8] The changes of these structure might cause abnormal increase in IOP. However, the reasons for these changes were not clarified. Many studies have found that sympathetic excitation might be associated with the changes in IOP,[9–11] so we speculated that the SC and TM might have the foundation to receive innervation from the autonomic nervous system to adjust their status. In our previous studies, we have found that there was a relationship between glaucoma and the Locus Coeruleus (LC), which was a major source of norepinephrine released in the brain. Both the patients with POAG and animal models of glaucoma showed anomalies in LC.[12] Our recent studies also showed that the SC and TM might have autonomic regulatory functions related to autonomic

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MY and ZC contributed equally to the work presented here and should therefore be regarded as equivalent authors.

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nervous system: Aerobic exercise could cause sympathetic nerve stimulation, consequently causing the expansion of the TM and SC, which, in turn, led to IOP reduction[13]; After performing the water-drinking test (WDT),which might cause parasympathetic nervous system stimulation, could lead to the collapse of SC, which resulted in increased IOP.[14] These are the foundations of our research to investigate the effect of adrenaline in lowering IOP.

Catecholamine adrenaline is an old drug for glaucoma treatment which acts primarily by improving outflow facility. Topical adrenaline preparations are known to reduce IOP without the incapacitating side-effects of accommodative spasm and miosis.[15] However, its detailed pharmacological effects on outflow facility remains unclear. According to our speculation, adrenaline might act as neurotransmitters of sympathetic nerves, changing the morphology of SC and TM to reduce outflow resistance.

Optical coherence tomography (OCT) is a non-invasive technique that can detect microstructural changes in the anterior chamber angle in vivo. With advances in the acquisition speed and imaging resolution, both SC and the TM can be identified continuously and dynamically.[16] Therefore, in this study, we attempted to observe the structural changes in human SC, TM, and anterior chamber parameters in normal eyes after application of 1% adrenaline using swept-source OCT, which may deepen our understanding of the mechanism in IOP lowering effect of adrenaline.

2. Subjects/materials and methods

2.1. Subjects

Participants were enrolled from the Department of Ophthalmology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The research was approved by the Institutional Review Board and followed the tenets of the *Declaration of Helsinki*. All subjects signed informed consent forms. All subjects underwent complete ophthalmologic examinations including best-corrected visual acuity (BCVA), refractive error, IOP (non-contact tonometer; NIDEK RT-2100; NIDEK, CO., LTD., Gamagori, Japan), central corneal thickness (CCT), and axial length (AL) as well as a slit-lamp examination and fundus examination. AL measurement was performed using an IOLMaster (Carl Zeiss, Inc., Jena, Germany). Healthy volunteers without ocular diseases with a BCVA of 20/25 or better, a refractive error between +3.0 and −6.0 D, IOP between 10 and 21 mmHg, and normal optic disc and retina were included.

2.2. OCT data acquisition and processing

In addition to an ocular examination, all participants underwent examinations with swept-source OCT (CASIA SS-1000; Tomey Corporation, Nagoya, Japan), which is specifically designed for anterior segment imaging using a 1310-nm wavelength, scan speed of 30,000 A-scans per second, and axial resolution of less than 10 μm. Each participant was given 1% adrenaline in the right eye. The examination was performed just before and after application of the adrenaline at 15, 45, and 90 minutes. The eyes were imaged in a dark room by the same examiner. For each participant, the scan was performed independently for the nasal and temporal quadrants (3 o'clock and 9 o'clock positions) of the right eye. Seated subjects were instructed to stare at one of four peripheral fixation lights ensure that the iridocorneal angle was centered in the instrument's field of view. If necessary, the operator assisted in opening the eyelid while taking care to avoid pressing on the eye. Scans of each site were repeated 3 times, and 3 images of each site centered at the 3 and 9 o'clock positions were chosen for the final analysis.

The SC was defined as observable when a thin, black, lucent space was found on the images (Fig. 1). For each image, in individuals with SC visibility, the SC diameter and area and TM width and thickness were assessed and then quantified manually using ImageJ software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD). The scleral spur (SS) was defined as the point between the TM and the ciliary body. The SC diameter was measured from the posterior to anterior SC endpoints, and the longest measurement between the 2 points was designed as the SC meridional diameter (Fig. 1). The SC area was drawn freehand and depicted as the area surrounded by the outline of the SC (Fig. 1). The TM width was defined as the distance between the SS and Schwalbe line (Fig. 1). Each TM thickness measurement was made perpendicular to the inner layer of the meshwork. The TM thickness was calculated as the average of 2 measurements made at the anterior endpoint of SC and halfway down SC (Fig. 1). The anterior chamber depth (ACD) was defined as the perpendicular distance between the corneal endothelium at the corneal apex and the anterior lens surface. Pupil diameter (PD) was measured as the distance from one side to the opposite side of the pupillary tip of the iris on the images by ASOCT.

2.3. IOP measurement

IOP was measured before and after the application of adrenaline at 15, 45, and 90 minutes using a noncontact tonometer device (NIDEK RT- 2100; NIDEK, CO., Ltd). In total, 3 measurements were obtained and the average IOP was recorded.

2.4. Statistical analysis

All analyses were performed using the SPSS software package version 19.0 (SPSS, Inc., Chicago, IL). Data are presented as the mean ± standard deviation where applicable. Paired sample *t* test was used for comparisons of the parameters after the administration of adrenaline at 3 time points respectively with those before administration within each subject. The test was 2-tailed and statistical significance was defined as $P < .05$.

3. Results

In total, the study included 15 normal subjects (7 male subjects and 8 female subjects; age range, 22–40 years). The general information and ocular characteristics were shown in Table 1.

In all individuals with SC visibility, the SC diameter varied from 112.79 μm to 310.30 μm in the 2 different quadrants of the eyes and the SC area ranged from 2410.79 μm^2 to 9107.44 μm^2.

Compared to the basal level (before application), both the SC diameter and SC area increased significantly after application of the adrenaline at the 3 time points (15, 45, and 90 minutes), with a maximum at 45 minutes and decreased slightly at 90 minutes. (Table 2, Fig. 2)

The TM width ranged from 518.71 μm to 1018.19 μm in the 2 different quadrants of the eyes. And the TM thickness ranged from 75.65 μm to 237.88 μm. The TM width increased with mild significance after application of the adrenaline at 15 and

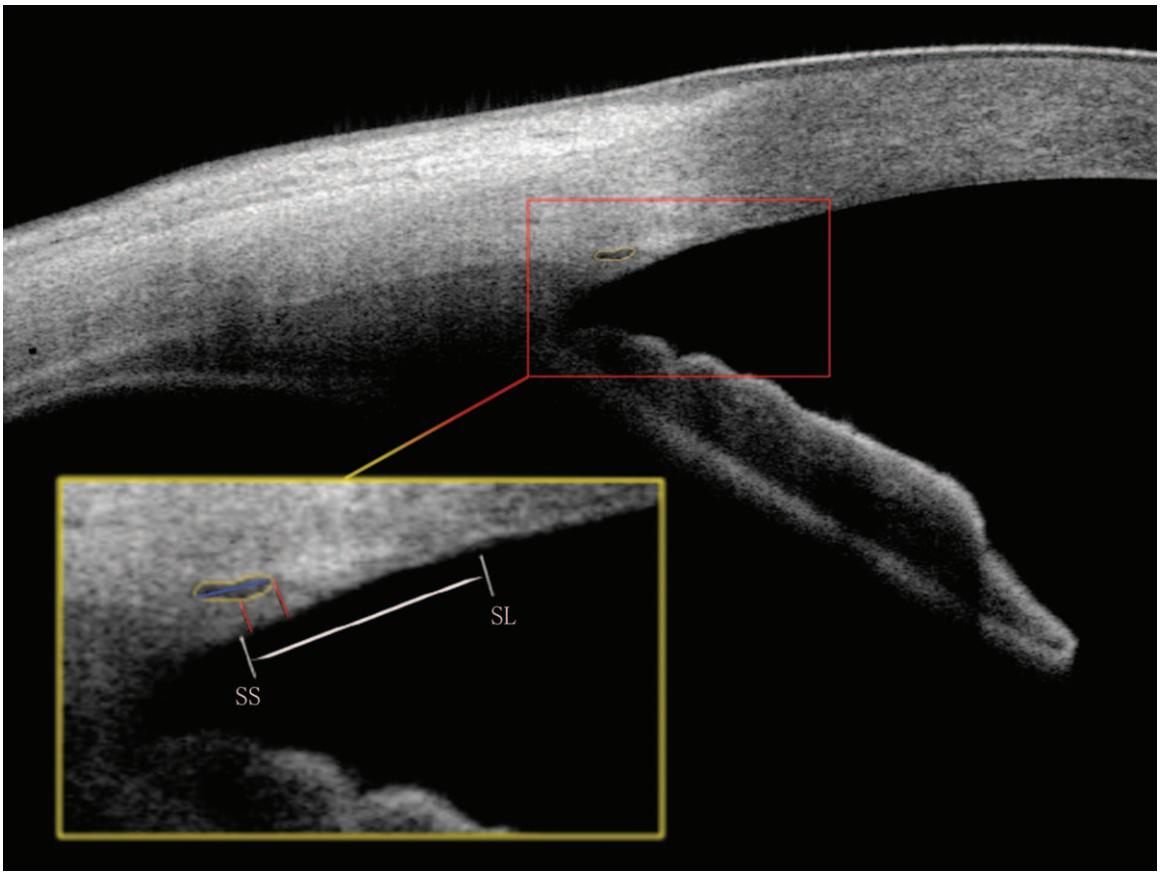

Figure 1. Example of SC and TM measurements made using the swept-source optical coherence tomography. The black oval space shows SC. The SC diameter: from the anterior to the posterior end point of SC (blue arrow). The SC area: drawn freehand and depicted as the area surrounded by the outline of the SC (yellow outline). The TM width: the distance between the SS and SL (white arrow). The TM thickness: 2 measurements made at the anterior endpoint of SC and halfway down SC (red lines), the average of them is calculated as TM thickness. SC = Schlemm's Canal, SL = Schwalbe line, SS = scleral spur, TM = trabecular meshwork.

45 minutes,while there was no significant change in TM thickness at the 3 time points (15, 45, and 90 minutes) compared with basal level (before application) (Table 3).

After application of adrenaline, there was also a significant decrease in mean IOP at the 3 time points, from 15.21 ± 2.78 mmHg (before application) to 13.82 ± 2.86 mmHg (90 minutes) (Table 4). The ACD ranged from 2.20 mm to 3.69 mm and the PD ranged from 3.05 mm to 6.04 mm. Both of the 2 parameters had no significant change at any time point after the application (Tables 5 and 6).

Table 1

Subject and ocular characteristics.

Parameters	Data
Mean age (yr)	29.1 ± 6.1
Male/Female	7/8
Preoperative IOP (mmHg)	15.21 ± 2.78
AL (mm)	24.69 ± 1.58
CCT (um)	534.60 ± 26.99
ACD (mm)	3.07 ± 0.35
PD (mm)	4.74 ± 0.82

Data are presented as mean ± SD.
ACD = anterior chamber depth, AL = axial length, CCT = central corneal thickness, IOP = intraocular pressure, PD = pupil diameter.

4. Discussion

Our study demonstrated that both the SC diameter and area increased after application of adrenaline, along with a mild

Table 2

Mean SC diameter and area before and after application of adrenaline.

SC diameter (um):				
	Nasal	*P* value*	Temporal	*P* value*
Before	203.48 ± 27.94	—	181.95 ± 35.27	—
15 min	239.69 ± 35.41	**.010**	220.37 ± 39.67	**.000**
45 min	229.61 ± 44.97	**.012**	219.66 ± 47.44	**.012**
90 min	206.54 ± 39.14	.972	216.00 ± 46.21	**.015**
SC area (um^2):				
	Nasal	*P* value*	Temporal	*P* value*
Before	3990.83 ± 950.72	—	4003.38 ± 1298.35	—
15 min	5166.61 ± 1037.59	**.001**	4850.23 ± 1524.08	**.000**
45 min	5650.25 ± 1280.35	**.000**	5622.51 ± 2006.40	**.001**
90 min	4885.26 ± 1431.38	**.026**	4896.18 ± 1637.23	**.009**

Data are presented as mean ± SD.
SC = Schlemm canal.
* The data at each time point was compared with the baseline (before). Paired *t* test was used to test statistical significance, bold face indicates a statistically significant difference, $P < .05$.

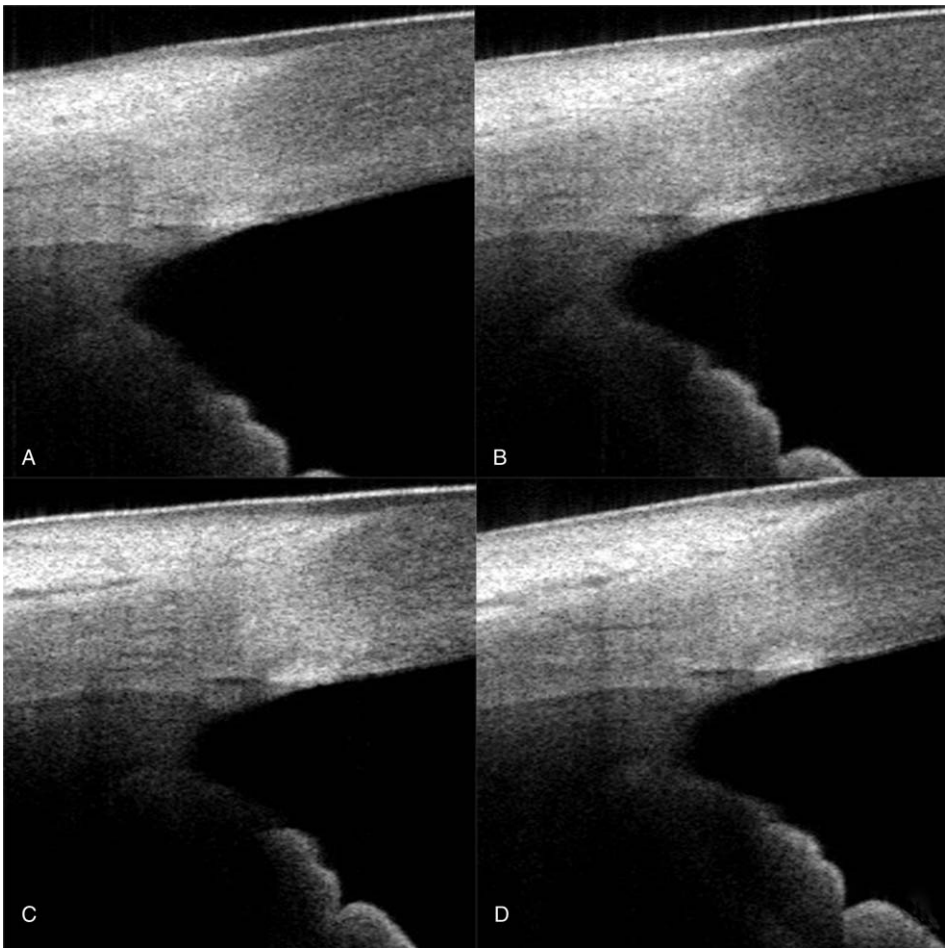

Figure 2. The SC and the TM morphology manifestation. before (A) and after application of adrenaline at 15 min (B), 45 min (C) and 90 min (D). SC = Schlemm's Canal, TM = trabecular meshwork.

increase in width of TM. To our knowledge, this is the first in vivo study to report the changes in SC and TM biometric parameters after application of adrenaline using swept-source OCT in normal individuals. Adrenaline, acting as agonist for bothα-and,β-adrenergic receptors, is an old and widely accepted drug for lowering IOP with complex pharmacological effects in human eyes.[17] Endogenous adrenergic amines produced by the sympathetic innervation in the eye have been found to modify the following 3 ocular processes: aqueous humor formation, uveal blood flow, and aqueous humor outflow.[18] The rate of aqueous humor production is determined by blood flow to the ciliary body and its rate of active secretion from the ciliary epithelium. Aqueous humor outflow is determined by resistance at the iridocorneal angle, the outflow facility of the trabecular

Table 3

Mean TM thickness and width before and after application of adrenaline.

TM thickness (um):				
	Nasal	***P* value***	**Temporal**	***P* value***
Before	140.02 ± 36.49	—	131.6507	—
15 min	147.64 ± 38.06	.104	133.8542	.533
45 min	149.96 ± 42.71	.106	138.0201	.342
90 min	141.89 ± 31.32	.097	133.5625	.527
TM width (um):				
	Nasal	***P* value***	**Temporal**	***P* value***
Before	781.53 ± 121.72	—	824.3878 ± 72.45	—
15 min	835.69 ± 103.64	**.049**	873.9390 ± 67.37	**.021**
45 min	849.79 ± 95.32	**.030**	873.1474 ± 77.89	**.022**
90 min	815.06 ± 101.02	.696	818.3944 ± 119.91	.787

Data are presented as mean ± SD.

TM = trabecular meshwork.

* The data at each time point was compared with the baseline (before). Paired *t* test was used to test statistical significance, bold face indicates a statistically significant difference, $P < .05$.

Table 4

Mean IOP before and after application of adrenaline.

	IOP (mmHg)	***P* value***
Before	15.21 ± 2.78	—
15 min	13.99 ± 2.95	**.001**
45 min	13.92 ± 2.98	**.003**
90 min	13.82 ± 2.86	**.001**

Data are presented as mean ± SD.

IOP = intraocular pressure.

* The data at each time point was compared with the baseline (before). Paired *t* test was used to test statistical significance, bold face indicates a statistically significant difference, $P < .05$.

Table 5

Mean anterior chamber depth before and after application of adrenaline.

	ACD (mm)	*P* value*
Before	3.07 ± 0.35	—
15 min	3.05 ± 0.35	.126
45 min	3.05 ± 0.34	.181
90 min	3.06 ± 0.36	.537

Data are presented as mean± SD.
ACD = anterior chamber depth.
* The data at each time point was compared with the baseline (before). Paired *t* test was used to test statistical significance, bold face indicates a statistically significant difference, $P < .05$.

meshwork and SC for the conventional route, the uveoscleral outflow facility for the unconventional route, and by the resistance of the episcleral venous circulation.[19]

Previous studies have focused on the effect of adrenaline on aqueous humor formation from ciliary body, suggesting that topical administration of adrenaline can reduce both the blood flow to the ciliary body[9,10] and active secretion of it,[20,21] thus reduces IOP. Besides, aqueous humor outflow is an essential site to modulate IOP, and our study mainly focused on this outflow facility of the trabecular meshwork and SC morphologically. Aqueous humor passes primarily through conventional route via the iridocorneal angle, that is, from the trabecular meshwork (TM) to SC and eventually reaching the episcleral venous circulation. Resistance at the TM and SC determines the efficiency of aqueous humor outflow in the conventional route, thus affecting the IOP.[22]

In our study, we observed that there was no significant mydriasis effect after application of adrenaline, suggesting that adrenaline at our experimental concentration did not effectively acts on the iris, where the alpha1-adrenoreceptor was distributed to the dilator pupillae causing mydriasis, which was known to reduce the outflow resistance via pupil constriction.[23] We discovered significant increase in the size of SC and mild stretch in TM width, which might give possible explanation of an increased outflow capacity thus underlying the decrease of IOP. It has been widely accepted that the contraction of the ciliary muscle through voluntary accommodation results in an immediate conformational change of the trabecular meshwork and possibly dilation of SC leading to a decreased outflow resistance of this route.[19] Studies of trabecular meshwork cells have also confirmed their contractile property, and their contraction increases aqueous humor outflow facility.[24,25] However, there is a contradiction that the contraction of ciliary muscle is cholinergic response and the stimulation of adrenergic nerve lead to relaxation of it. A more recent study states that the sympathetic system only slightly affects the dynamics of accommodation and has little effect on the resting level or amplitude of accommodation.[26] In addition, there was no significant change in ACD after application of adrenaline in our study, which was consistent with steady state of iris and ciliary body discussed above. So the changes in TM and SC after topical adrenaline may not be well explained through the view of ciliary muscle traction. Notably, it has been reported that there is autonomic nervous system directly controlling trabecular meshwork and SC resistivity, through which noradrenaline appears to increase trabecular meshwork outflow facility.[19] Previous studies have found that sympathetic nerve fibers and their neurotransmitter receptors are widely distributed in the aqueous humor outflow pathway and beta2-adrenergic receptors have been detected in the TM and SC.[11,27–29] Alvarado et al found that adrenaline and isoproterenol decreased the outflow resistance through the paracellular pathway of schlemm's canal endothelial and TM cells through a beta-receptor mediated response that widens the intercellular space and therefore reduces cell area.[28] In addition, Zhou et al found that drugs which typically increase outflow resistance systematically caused cell stiffness to increase, while in most cases, those drugs such as Isoproterenol which typically decrease outflow resistance caused cell stiffness to decrease. What is more, they also observed that the beta2- adrenergic receptor protein level positively correlated with the degree of relaxation triggered by isoproterenol.[29] Our recent study also showed that SC and the TM may have autonomic regulatory functions and their expansion and collapse may not be completely dependent on the IOP.[13,14] The results of our study was consistent with such researches, and the deformation of SC and TM is more likely induced by direct control of such autonomic nerves. While autonomic nervous system in TM and SC needs further investigation, our in vivo study gives support to this perspective. According to our findings, we supposed that there might be adrenergic fibers direct projection to TM and SC regions thereby modulating the resistance of outflow facilities. In our study, topical administration of adrenaline could enhance sympathetic nerve activity thus led to SC expansion, consequently causing the IOP to decrease.

Table 6

Mean pupil diameter before and after application of adrenaline.

	Pupil diameter (mm)	*P* value*
Before	4.74 ± 0.82	—
15 min	4.46 ± 0.74	.165
45 min	4.61 ± 0.76	.418
90 min	4.27 ± 1.38	.186

Data are presented as mean± SD.
* The data at each time point was compared with the baseline (before). Paired *t* test was used to test statistical significance, bold face indicates a statistically significant difference, $P < .05$.

However, the present study has certain limitations. First, we only made such speculation through morphological changes of SC and TM, the underlying cellular and molecular mechanism through which the sympathetic nervous system affects aqueous outflow facilities is rather complicated and needs further study. A large number of basic experiments are underway. Second, all participants in the present study were healthy individuals, and glaucomatous patients should be taken into consideration in future studies. The problem is that patients with glaucoma more or less have already received anti-glaucoma treatments, which may affect the parameters of SC and trabecular meshwork (TM). On the other hand, considering glaucomatous patients' compliance and psychological acceptance, the data of glaucoma patients is temporarily difficult to obtain. Third, our sample size was relatively small, so there might be some confounding factors affecting the results in this preliminary study. We should increase the sample size in the future studies to make the results more credible.

Regulation of IOP by the conventional (trabecular) outflow pathway is complicated, involving a myriad of mechanical and chemical signals.[30] Our study targets at the outflow facilities, especially the TM and SC, which may improve our the understanding of autonomic control of IOP. In-depth research in such mechanism of outflow regulation will contribute to the treatment of glaucoma.

Author contributions

Conceptualization: Wei Chen.
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Methodology: Zhiqi Chen.
Project administration: Hong Zhang.
Resources: Mu Li.
Validation: Junming Wang.
Visualization: Mu Li.
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