• Clinical Research •

# Efficacy, safety and IOP-lowering mechanisms of ultrasound cycloplasty for angle-closure glaucoma

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## Abstract

● **AIM:** To evaluate the short-term efficacy and safety of ultrasound cycloplasty (UCP) procedure in Chinese patients with angle-closure glaucoma (ACG), and the mechanisms of its intraocular pressure (IOP) lowering effects.

● **METHODS:** Fifty-six patients (56 eyes) diagnosed with primary and/or secondary ACG were enrolled in this prospective study. Visual acuity, IOP, slit-lamp examinations, structural parameters of anterior segments including anterior chamber depth (ACD), pupillary diameter (PD), anterior chamber area (ACAr), anterior chamber angle (ACAn), and side effects were evaluated. Seven rhesus macaques (*Macaca Mulatta*) were used for the analyses of IOP lowering effects, including inflammatory reactions, pathohistological evaluation, scanning electron microscopy (SEM), and aqueous outflow pathway *via* 1% basic fuchsin perfusion.

● **RESULTS:** Fifty six eyes of 24 male and 32 female patients with an average age of 58.93±15.97 years old were recruited in primary and secondary ACG affected 31 and 25 eyes, respectively. Clinically, the mean IOP was 17.89±7.93 mm Hg (*n*=53, 53.63% reduction, *P*<0.001) at 1wk and 22.47±12.00 mm Hg at 12mo (*n*=16, 18.67% reduction, *P*<0.01) after UCP, compared to the baseline of 39.08±14.75 mm Hg (*n*=56). Postoperative tolerance was favorable in 94.64% of cases, with visual acuity unchanged or improved in 96.43% of patients. Mild and transient inflammatory reactions were observed post UCP. UBM analysis revealed statistically significant changes in anterior chamber parameters: increased ACD (*n*=22, *P*<0.05), enlarged PD (*n*=22, *P*<0.05), expanded ACAr (*n*=16, *P*<0.01), and widened ACAn (*n*=19, *P*<0.05) compared to preoperative measurements. As in normal monkey eyes, IOP was also reduced upon UCP. Mild inflammatory reactions were seen 1-7d post treatment. Hematoxylin and Eosin (H&E) staining showed enlarged spaces among ciliary muscle bundles. Ciliary process stromal edema was evident, but significant loss of two layers of ciliary epitheliums was not seen. SEM confirmed ciliary muscle fibers concentrated. Fuchsin anterior chamber perfusion showed the whole ciliary body staining in UCP group, but only surface staining in controls.

● **CONCLUSION:** UCP is efficient and safe to lower the IOP of patients with ACG. Changed anterior chamber structure and increased aqueous humour outflow *via* uveoscleral pathway may significantly attribute to IOP lowering effects of UCP.

● **KEYWORDS:** efficacy; safety; mechanisms; ultrasound cycloplasty; angle-closure glaucoma

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## INTRODUCTION

As the leading cause of irreversible blindness in the world, glaucoma is characterized by retinal ganglion cell loss and optic nerve degeneration[1-2]. Although the pathogenesis of glaucoma is not fully understood, elevated intraocular pressure (IOP) is the main risk factor for this condition[1-2]. Therefore, IOP-lowering therapy is the primary treatment for this disease[3-5]. It is the only evidence-based

treatment to effectively delay the progression of glaucomatous optic neuropathy[5-6].

Ocular hypotensive medications decrease IOP by reducing aqueous humor (AH) production or by increasing its outflow[7-9]. Ultrasound cycloplasty (UCP) should be classified in the category of treatments that reduce AH generation owing to the objective of its design. Similar to cyclocryotherapy and trans-scleral diode laser photocoagulation, UCP is a cyclodestructive procedure that uses high-intensity focused ultrasound technology[10-12].

UCP is a newly developed, minimally invasive glaucoma surgical technique designed to act through the selective coagulation of the ciliary body and the reduction of AH production[13-15]. First, a miniaturized equipment called EyeOP1 allows treatment of the whole circumference through a one-step procedure designed and promoted by Eye Tech Care (Rillieux-la-Pape, France)[16]. Using this equipment, high-frequency ultrasound can be focused on the ciliary body through a coupling cone and treatment probe site, whose design is based on the geometry of the eye. Three probe sizes (11-, 12-, and 13-mm ring diameters) ensure proper eye fit for variable eye sizes in different patients. The transducers align along an 11–13 mm circle in the treatment probe, focusing on the sclera 2 mm below the ciliary body for precise targeting. The six transducers emit ultrasound at 21 MHz with an acoustic power of 2 W, rapidly heating the targeted local ciliary body to 90°C (without causing tissue boiling) and enabling treatment of up to 30% of its tissue. By turning the treatment probe around at a fixed angle that was preset with the coupling cone, up to 10 focus treatment sites can be generated[13-15].

Theoretically, UCP should be classified as an antiglaucoma treatment that reduces AH production because of the objective of its design. However, previous studies have shown that increasing AH outflow, rather than reducing its production, may also play a role in UCP's IOP-lowering effects of UCP[14,17-18]. Unfortunately, there is not enough evidence to support this hypothesis.

In this prospective study, UCP was performed on 56 eyes of patients with primary or secondary angle-closure glaucoma (ACG). Changes in IOP and the anterior segment of the treated eyes, along with the side effects, were evaluated. In addition, UCP was performed on monkey eyes with normal IOP. Clinical examination, hematoxylin and eosin (H&E) staining, tissue staining with 1% basic fuchsin anterior chamber perfusion, and scanning electron microscopy (SEM) were used to investigate the mechanisms underlying the IOP-lowering effects of UCP.

## PARTICIPANTS AND METHODS

**Ethical Approval** This study was approved by the Medical Ethics Committee of Xiamen Eye Centre (XMYKZX-KY-2023-024) and Research Ethics Committee of Shenzhen People's Hospital (2023-396-01). Informed consents were obtained from the subjects in written, and no participant received a stipend. All animal experiments were approved by the Ethics Committee of the Institute of Laboratory Animal Sciences, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital (Lunshen2023/006), and conformed to the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research.

**Participants** Totally 56 patients treated with UCP were recruited at the Xiamen Eye Center and Shenzhen People's Hospital between January 2021 and April 2024. The inclusion criteria were as follows: 1) Age between 18 and 90 years old; 2) IOP>21 mm Hg (with or without antiglaucoma medication); 3) primary or secondary ACG. The exclusion criteria were as follows: 1) patients with active ocular inflammation; 2) pregnant or lactating women; 3) ocular disease other than glaucoma that may affect the assessment of visual acuity and/or IOP (including choroidal hemorrhage or detachment, lens subluxation, thyroid ophthalmopathy, and clinically significant macular edema); 4) patients who underwent other antiglaucoma surgeries to reduce IOP within 6mo.

Each patient underwent routine preoperative examination, including uncorrected/best-corrected visual acuities, photography of the anterior chamber, perimetry, fundus photography, IOP (Icare tonometer), ultrasound biomicroscopy (UBM), biometric parameters of the eyeball [axial length (AL), white-to-white distance, and central corneal thickness (CCT)], and optical coherence tomography (OCT).

Postoperative follow-up visits took place at 1d, 1wk, 1, 3, and 6mo after treatment. Visual acuity and IOP were measured in all patients, and possible complications were recorded at each visit.

**Ultrasound Biomicroscopy Examination** UBM (Aviso UBM, Quantel Medical, Auvergne Cedex, France) examination[19] was performed by an experienced technician one day before and one week after surgery. Anterior parameters included the anterior chamber depth (ACD), CCT, anterior chamber width (ACW), lens vault (LV), pupil diameter (PD), ciliary process-ciliary process distance (CP-CP distance), anterior chamber area (ACAr), anterior chamber angle (ACAn) and angle-opening distance at 500 μm (AOD 500). Clear UBM images were measured quantitatively by the same operator using a caliper in the UBM software. The AOD500 and ACAn were measured by an experienced examiner using CorelDRAW software (Alludo, Ottawa, Canada). ACAr was quantitatively measured by the same examiner using Image J software (National Institutes of Health, Maryland, USA). ACD was defined as the axial distance between the endothelial layer of the cornea and the anterior surface of the lens. CCT was

defined as the thinnest distance from the anterior vertex of the cornea to the posterior surface of the cornea. ACW was defined as the width between the two scleral spurs. The LV was defined as the perpendicular distance from the top of the lens to the horizontal line between the scleral spurs. PD was defined as the distance between the pupil edges of the iris cross sections. The CP-CP distance referred to the distance between the ciliary processes on both sides. ACAr represents the area ($mm^2$) contained within the corneal endothelium, anterior surface of the iris, and anterior surface of the lens (within the pupil). ACAn indicates an angle formed with the apex at the iris recess and the arms passing through the point on the meshwork 500 μm from the scleral spur and the point on the iris perpendicularly opposite. The AOD 500 represents the distance between the point of the corneal endothelium 500 μm from the scleral spur and the anterior iris surface. An appropriate probe for each tested eye was selected by merging the white-to-white range of the UBM as previously described[19-20]. In addition, possible inflammation in the anterior segments after UCP was examined by UBM.

**Surgery** UCP surgeries were performed using the EyeOP1 device (Eye Tech Care, Rillieux-la-Pape, France), which consists of a single-use sterile pack, including a coupling cone and treatment probe, and a compact operator console. Three probe sizes are available: 11, 12, and 13 mm. The size of the probe was selected on the basis of the biometric parameters of each patient (AL and white-to-white distance). The UCP treatment protocol can be performed in six, eight, and ten sectors. The specific parameters of the ultrasound equipment were set as follows: operating frequency (21 MHz), acoustic power (2.45 W), ultrasound exposure time per sector (8s), and sequential sector activation interval (20s).

The UCP was performed by the same experienced glaucoma expert. All patients were administered retrobulbar anesthesia. All UCP treatments followed a previously reported UCP protocol for JoVE[14]. After adjusting the operating eye to a horizontal position, the polymer coupling cone was placed vertically right in the middle of the eye and held in place by negative pressure, and the treatment probe was inserted into the cone to ensure proper transducer alignment. The cavity formed by the cone, eye, and probe was filled with saline through a central port, and saline levels were replenished as needed in cases of leakage during the procedure. Sequential activation of the six transducers was initiated while maintaining a negative pressure. The probe was rotated by a fixed angle when more than six treatment sites were required. Following an audible click, the treatment was restarted according to on-screen guidance. Throughout the procedure, all movements were prohibited, and optimal positioning was rigorously maintained.

**Postoperative Treatment** All patients were treated with conventional antibiotics and anti-inflammatory drugs within 1mo after surgery, including levofloxacin eye drops (Cravit eye drops, four times a day), prednisolone acetate ophthalmic suspension 1% (Pred Forte, four times a day). and tobramycin and dexamethasone eye ointment (Tobradex, once every night). IOP was measured using an Icare tonometer (Icare, Finland, Espoo, Finland) at each visit. Patients whose IOP remained at >21 mm Hg continued to use preoperative IOP-lowering drugs.

**Animals** Seven male adult rhesus monkeys (*Macaca mulatta*) from the same institute were kept in individual, spacious, dedicated cages, housed in a 22°C thermostatic room with a 12h/12h light/dark cycle. Sterilized food and drinking water were provided *ad libitum*.

**Animal modeling** UCP modeling of monkeys under general anesthesia followed the same protocol as the patients. Animals were anesthetized by intramuscular injection of 5% Zoletil50 (Virbac Lab, Carros, France) at a dose of 10 mg/kg. One randomly selected eye was subjected to 10 sections of UCP surgery, as described above. The contralateral eye served as the negative control and did not receive any treatment. Postoperative treatments for the animals were the same as those for the patients.

**Animal IOP measurement** Normal-tension animal IOP readings were measured before modeling as described previously[21]. Monkeys' IOP was measured at 5min after anesthesia (5% Zoletil50, 10 mg/kg), by a masked investigator using the TonoVet rebound tonometer (Icare, Finland, Espoo, Finland).

**Animal UBM scanning** The animals underwent UBM (Meda, Tianjin, China) examination similar to the patients for UCP probe selection and postoperative inflammation assessment. However, the ACD, CCT, ACW, LV, PD, CP-CP distance, ACAr, and AOD 500 parameters were not analyzed.

**Animal slit-light microscope examination** After each IOP measurement, slit-light microscopy was performed to check for any abnormalities in the treated eyes. Routine animal anterior segment photographs were obtained using a slit-lamp biomicroscope (S350; Shanghai MediWorks Precision Instruments, Hangzhou, China) equipped with an attached camera (EOS 600D; Canon, Tokyo, Japan).

**Histology analysis** Two randomly selected monkeys were euthanized for histological analysis on day four after repeated UCP treatment, which was performed after the last IOP measurement. The eyeballs of one monkey were removed immediately after termination of the Hematoxylin and Eosin (H&E) study, and temporal and nasal orientations were marked to ensure that the sections involved the treated sites. Paraffin sectioning and H&E staining were performed following the protocol as described in a previous study[21].

The other monkey was subjected to 1% fuchsin basic anterior chamber perfusion staining after euthanasia. Fuchsin solution was injected into both eyes of the UCP-treated and negative controls, and a water column pressure of 50 cm was maintained for 5min. Next, 500 mL Phosphate-Buffered Saline (PBS) was injected into each eye to flush out unbound fuchsin. The eyeballs of the perfused monkeys were harvested for paraffin sectioning after euthanasia, following a previously described protocol[21]. Fuchsin stained sections were photographed directly under a light microscope.

**Scanning electron microscope** UCP-treated and control eyeballs harvested from sacrificed monkeys were carefully cut to collect 3 mm×3 mm ACAn tissues. These tissues were washed twice in PBS, fixed in 3% glutaraldehyde in PBS (pH 7.0), and sent to Chengdu Lilai Biomedicine for scanning electron microscopy (SEM) analysis. A JSM-IT700HR SEM (Japan Electron Optics Laboratory Co., LTD, JEOL, Tokyo, Japan) was used.

**Statistical Analysis** Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, Boston, MA, USA) and SPSS statistical software (SPSS Inc., Chicago, Illinois, USA). The Shapiro-Wilk test was used to check if the data were normally distributed. If so, statistical significance was determined using a *t*-test. Otherwise, nonparametric statistics were used. Statistical significance was set at $P<0.05$.

## RESULTS

**Short Term Efficacy and Safety of UCP** This study included 56 eyes from 56 patients (Table 1). As the follow-up period increased, the number of patients gradually decreased. Only two patients (3.57%) experienced pain during the UCP procedure and one patient (1.79%) experienced pain within 12h after surgery. However, the pain disappeared one day after the surgery. Other patients (94.64%) did not experience pain before or after the surgery.

The patients' visual acuity is shown in Table 2. Only 3.57% of the patients had lower vision levels than the preoperative levels on day 1. A total of 96.43% of the patients showed no changes or varying degrees of improvement in visual acuity compared to their preoperative vision. Visual acuity improved significantly at week 1 and month 1.

The mean±SD IOP of the 56 patients before UCP treatment was 39.08±14.75 mm Hg. Table 3 shows the mean IOP and mean IOP reduction during the follow-up period. The mean IOP at each follow-up visit was significantly lower than at baseline ($P<0.01$). After UCP, IOP decreased by 42.25%–53.63%. The largest reduction from baseline in mean IOP was at 1wk post UCP treatment, which was recorded as 17.89±7.93 mm Hg ($n=53$, 53.63% reduction, $P<0.001$). At the 12-month follow-up, the mean IOP was 22.47±12.00 mm Hg ($n=16$, 18.67% reduction, $P<0.01$).

**Table 1 Basic information of patients** mean±SD or *n*

| Variable | *n*=56 |
|---|---|
| Age at time of surgery, y[a] | 58.93±15.97 |
| Gender[a] | |
| Male | 24 |
| Female | 32 |
| Type of glaucoma | |
| Primary ACG | 31 |
| Secondary ACG | 25 |
| Lens status | |
| Phakic | 44 |
| Pseudophakic | 9 |
| Aphakia | 3 |
| Frequency of previous glaucoma surgery | |
| Zero | 41 |
| One | 13 |
| Two | 2 |
| Type of previous glaucoma surgery | |
| Laser peripheral iridotomy | 10 |
| Laser iridoplasty | 3 |
| Glaucoma drainage implant | 2 |
| Glaucoma drainage implant+cataract surgery | 2 |
| Preoperative parameters | |
| IOP, mm Hg | 39.08±14.75 |
| Primary ACG IOP | 36.87±16.05 |
| Secondary ACG IOP | 41.82±12.74 |
| AL, mm | 23.01±1.65 |
| White-to-white, mm | 11.56±0.78 |
| UCP probe size used | |
| 11 mm | 10 |
| 12 mm | 31 |
| 13 mm | 15 |
| UCP treatment | |
| 6 sectors | 13 |
| 8 sectors | 6 |
| 10 sectors | 37 |
| Pre-operative glaucoma medications | |
| Eye drops | 2.37±0.97 |
| Tablets (acetazolamide)[a] | 18 |
| Antiglaucoma medications one year post UCP | |
| Eye drops | 0.94±1.03 (*n*=16) |
| Tablets (acetazolamide) | 1 |

Numbers are per eyes. [a]Numbers are per patients. IOP: Intraocular pressure; UCP: Ultrasound cycloplasty; AL: Axial length; ACG: Angle-closure glaucoma.

UBM analysis (Table 4) revealed statistically significant changes in anterior chamber parameters: increased ACD (2.10±0.91 mm to 2.20±0.88 mm, $n=22$, $P<0.05$), enlarged PD (3.94±1.07 mm to 4.36±0.92 mm, 10.66% increase, $n=22$, $P<0.05$), expanded ACAr (9.10±3.44 $mm^2$ to 10.05±3.02 $mm^2$, $n=16$,

**Table 2 Patients' visual acuity at each follow-up visit compared to preoperative vision** *n*

| Parameters | Patients quantity[a] | Unchanged | Improved | Worsened |
|---|---|---|---|---|
| Day 1 | 56 | 40 | 14 | 2 |
| Week 1 | 53 | 28 | 23 | 2 |
| Month 1 | 36 | 13 | 21 | 2 |
| Month 3 | 25 | 10 | 14 | 1 |
| Month 6 | 22 | 10 | 12 | 0 |
| Month 12 | 16 | 3 | 9 | 4 |

[a]Some patients were lost to follow-up.

**Table 3 Mean IOP at baseline and during follow-up visits** mean±SD

| Parameters | Patients, quantity[a] | IOP, (mm Hg) | Relative IOP, reduction[b] | *P*[c] |
|---|---|---|---|---|
| Baseline[d] | 56 | 39.08±14.75 | | |
| Day 1 | 56 | 22.57±8.56 | 42.25% | <0.0001 |
| Week 1 | 53 | 17.89±7.93 | 53.63% | <0.0001 |
| Month 1 | 36 | 19.63±8.68 | 52.60% | <0.0001 |
| Month 3 | 25 | 21.5±10.08 | 43.91% | <0.0001 |
| Month 6 | 22 | 20.24±8.79 | 46.96% | <0.0001 |
| Month 12 | 16 | 22.47±12.00 | 18.67% | 0.006 |

[a]Some patients were lost to follow-up. [b]Postoperative IOP was compared to baseline IOP of same patients. [c]Paired *t*-test comparison mean IOP baseline versus follow-up. [d]Baseline was defined as IOP before UCP treatment. IOP: Intraocular pressure; UCP: Ultrasound cycloplasty.

**Table 4 UBM parameters measured at baseline and 1wk post UCP treatment** mean±SD

| Parameters | Patients quantity | Baseline | Week 1 | *P*[a] |
|---|---|---|---|---|
| ACD (mm) | 22 | 2.10±0.91 | 2.20±0.88 | 0.0377 |
| PD (mm) | 22 | 3.94±1.07 | 4.36±0.92 | 0.0244 |
| ACAr ($mm^2$) | 16 | 9.10±3.44 | 10.05±3.02 | 0.0038 |
| ACAn (°) | 19 | 5.81±15.64 | 8.96±16.99 | 0.0121 |
| CP-CP distance (mm) | 22 | 9.50±0.68 | 9.45±0.79 | 0.5763 |
| ACW (mm) | 22 | 10.83±0.67 | 10.83±0.56 | 0.9920 |
| CCT (mm) | 22 | 0.57±0.10 | 0.54±0.06 | 0.1043 |
| LV (mm) | 22 | 0.90±0.36 | 0.84±0.29 | 0.4914 |
| AOD 500 (μm) | 19 | 0.07±0.23 | 0.10±0.23 | 0.0551 |

[a]Paired *t*-test comparison mean IOP baseline versus follow-up. ACD: Anterior chamber depth; PD: Pupil diameter; ACAr: Anterior chamber area; ACAn: Anterior chamber angle; CP-CP distance: Ciliary process-ciliary process distance; ACW: Anterior chamber width; CCT: Central corneal thickness; LV: Lens vault; AOD 500: Angle-opening distance at 500 μm.

*P*<0.01), and widened ACAn (5.81°±15.64° to 8.96°±16.99°, *n*=19, *P*<0.05) when compared to the preoperative values. These findings were confirmed by a slit-light examination (Figure 1). Other results, including the mean CP-CP distance, mean ACW, mean CCT, mean LV, and mean AOD 500, were not statistically significant.

Interestingly, except for the parameters shown above, UBM revealed a typical phenomenon that was beneficial for increasing outflow through the uveoscleral pathway: widening of the perichoroidal space (Figure 2).

There were few cases of postoperative complications. Eight cases of conjunctival congestion and 3 cases of anisocoria were detected. No serious complications, such as severe hypotony, phthisis bulbi, choroidal effusions, or hemorrhage, were observed.

**Monkey UCP Models** After 10 sections of UCP treatment, scheduled IOP measurements showed good IOP-lowering effects in monkeys. The detailed IOP curves are shown in Figure 3. As showed in Figure 3A, the mean IOP was deducted from 23.10±1.96 (baseline) to 9.67±2.85 (lowest). However, on day 21 after UCP treatment, the IOP curve showed a trend towards slow recovery without any antiglaucoma medication. Until day 140, there was no statistically significant difference in the mean IOP between the two groups.

Mild inflammation was observed in the UCP-treated eyes of monkeys, which disappeared completely within one week. As shown in Figure 3B and 3C, slight hyperemia and dilated pupils were observed in the tested eyes. Anterior chamber flares were detected in UCP-treated eyes from day 1 to day 7. No other serious adverse effects were observed. Additionally, UBM revealed dispersed points such as hyperechoic signals (Figure 3C) in the UCP-treated monkey eyes on day 3 post-surgery, and signals for ciliary body weakened after UCP treatment.

**H&E Staining of ACAn Tissue Sections** The H&E staining results of the ACAn tissue paraffin sections are shown in Figure 4. As shown in Figure 4A, the biggest change in the ciliary body structure was that the UCP-treated ciliary muscle gap became much wider than that of the control. Quantitative analysis of intermuscular spaces within the ciliary muscle was performed by delineating a 2000-μm linear axis from the scleral spur (Figure 4A) into the ciliary body, with three 300-μm diameter circular sampling zones along this axis. Image-Pro Plus software measured the pixel areas of muscular interstices across six sampled images per group, displayed as column charts in Figure 4A, which indicated that UCP-treated ciliary body muscular gaps had widened by at least 100%. The non-pigmented ciliary epithelial cells of the UCP-treated eyes remained relatively complete (Figure 4A).

**Scanning Electron Microscopy** The SEM results of UCP-treated or untreated ACAn tissues from monkeys are shown in Figure 4B, from which more concentrated ciliary muscle fibers and smoother corneal endothelial cells can be seen. These results were similar to those reported by Aptel *et al*[22].

**Fuchsin Staining of Anterior Chamber Perfusion Showing the Uveoscleral AH Outflow Pathway** A 1% fuchsin basic solution was used for anterior chamber perfusion staining in the monkey UCP models. The small molecule fuchsin could pass through UCP surgery, opening the uveoscleral AH outflow pathway, but could not penetrate that of the controls.

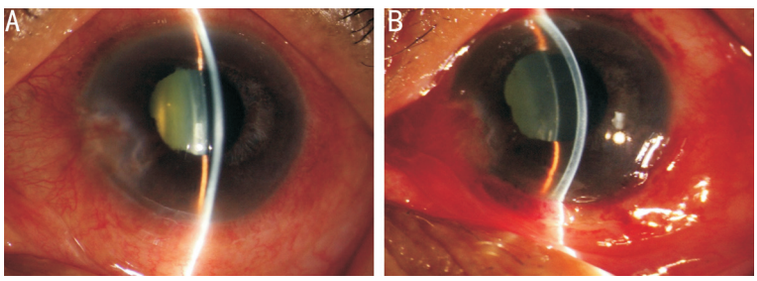


**Figure 1 Photography of the anterior segment of the same eye before (A) and day-1 after (B) UCP** It indicates the significant changes in central and peripheral ACD after UCP. UCP: Ultrasound cycloplasty; ACD: Anterior chamber depth.

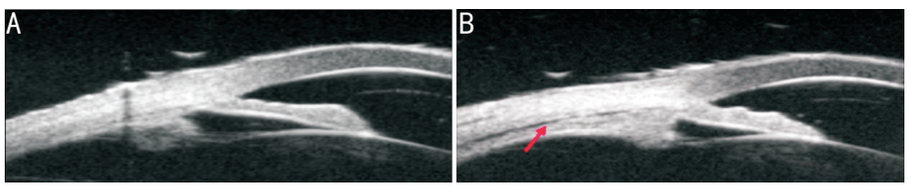


**Figure 2 Typical case of UBM with widen perichoroidal space (red arrow) after UCP** Preoperative (A) and week-1 postoperative (B) UBM images were showed in contrast. UCP: Ultrasound cycloplasty; UBM: Ultrasound biomicroscopy.

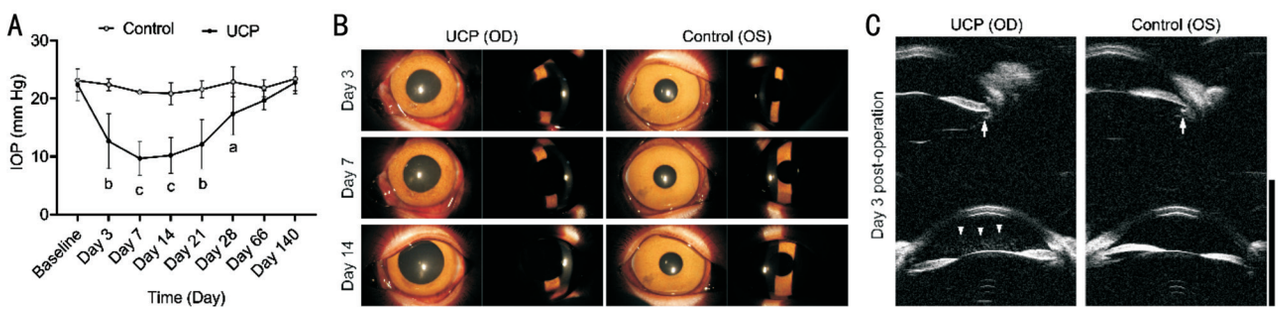


**Figure 3 Ophthalmological examinations of monkeys before and after UCP** IOP measurements, anterior segment slit-lamp examination findings, and UBM evaluation results were included. A: The temporal dynamics of IOP response in monkeys ($n$=7 at baseline and on postoperative days 3, 7, 14, 21, 28, and 66; $n$=6 on day 140) following UCP. Error bars represent SD, and the statistical significances were calculated using the two-tailed paired $t$-test. $^{a}P$<0.05, $^{b}P$<0.01 and $^{c}P$<0.001 versus control. B: Representative anterior segment images in monkeys post-UCP. C: Representative UBM images in monkeys following UCP. Arrows represented the anatomical location of ciliary body. The arrowheads designated discrete hyperechoic signals demonstrating homogeneous distribution patterns. Scale bar=10 mm. UCP: Ultrasound cycloplasty; IOP: Intraocular pressure; UBM: Ultrasound biomicroscopy; SD: Standard deviation.

As shown in Figure 5, fuchsin stained almost the entire ACAn tissues pink, including the entire trabecular meshwork (TM), part of the iris, ciliary body, non-pigmented ciliary epithelium, sclera, and subconjunctival space. In the control group, fuchsin stained only the TM, and a small part of the ciliary body near the TM in light pink.

## DISCUSSION

UCP is a minimally invasive glaucoma surgical technology designed to act through precise high-intensity focused ultrasound coagulation of the ciliary body and to reduce AH production[13-15]. The procedure is quick, noninvasive, and can be performed in a daycare setup. Unlike traditional cyclodestructive procedures such as cyclophotocoagulation and cyclocryotherapy, which cause significant pain and ocular inflammation reactions, UCP is gentler and more precise, and therefore causes less damage to the ciliary body structure[12]. IOP lowering effects of UCP have been proven to be efficient and safe in previous reports[20,23-25] and were confirmed in the current study both in patients and animals.

Wu *et al*[26] collected data from 19 articles and performed a Meta-analysis to evaluate the efficacy and safety of UCP. Their weighted mean difference (11.39, 95%CI, 9.88–12.90, risk of bias table, Review Manage 5.4, the Cochrane Collaboration) showed that patients had significant reductions in IOP after UCP treatment. Fewer postoperative complications were reported, and the risk ratio (RR) was 0.30 (95%CI, 0.19–0.49). Additionally, pain relief effects of UCP were confirmed, an RR of 3.06 (95%CI, 1.95–4.81). Their results indicated good efficacy and safety of the UCP procedure[26]. However, it must be mentioned that ocular hypotensive drops or tablets are also needed as supplementary medications after UCP, although the dosage and types of medication can be reduced to an acceptable range[24-25,27]. Additionally, in a long-term (2-year) study by Giannaccare *et al*[27], only 10.3% of UCP cases achieved

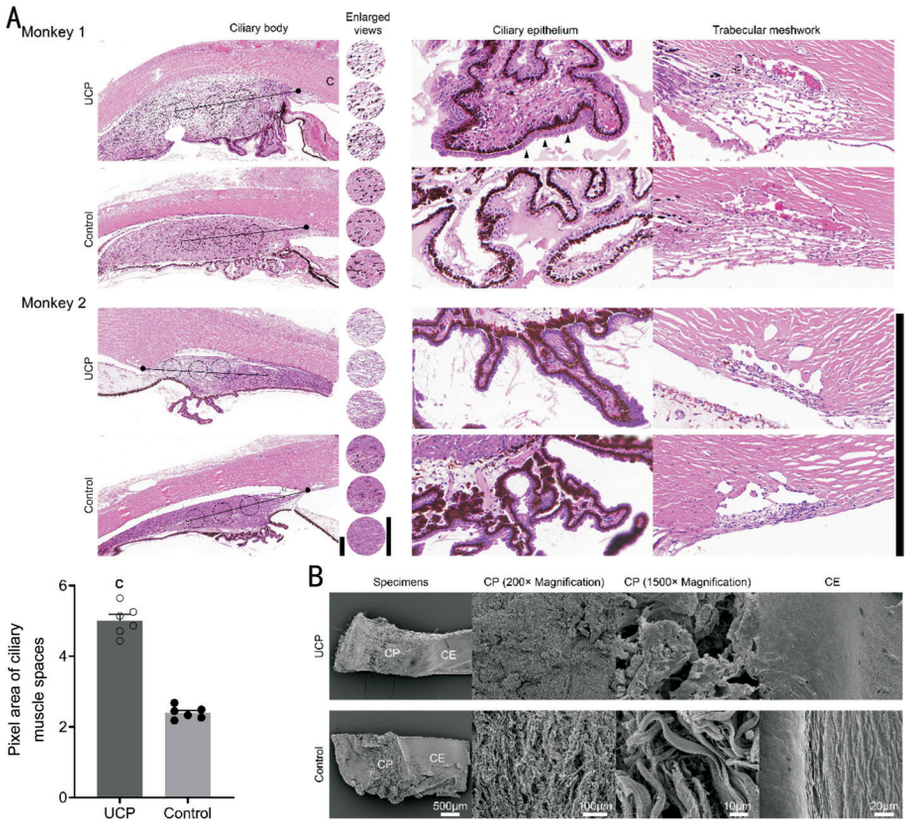


**Figure 4 Histomorphological analysis in the ACAn tissues of primates following UCP** A: Hematoxylin-eosin staining revealed structural alterations in the ACAn tissues, including the ciliary body, non-pigmented ciliary epithelium (black arrowheads), and trabecular meshwork, in two representative monkeys. Enlarged views of circular sampling zones, which were sampled as circles arranged in straight lines, indicated the widen intermuscular spaces of the CB. Error bars represent the standard error of the mean, and statistical significances were calculated using the two-tailed unpaired *t*-test. $^{c}P$<0.001 versus control. Scale bars=300 μm. B: SEM revealed ultrastructural alterations in the ciliary processes (CP), demonstrating flattened folds in UCP-treated eyes, whereas the corneal endothelium (CE) exhibited normal morphology. UCP: Ultrasound cycloplasty; CB: Ciliary body; C: Cornea; I: Iris; SEM: Scanning electron microscopy.

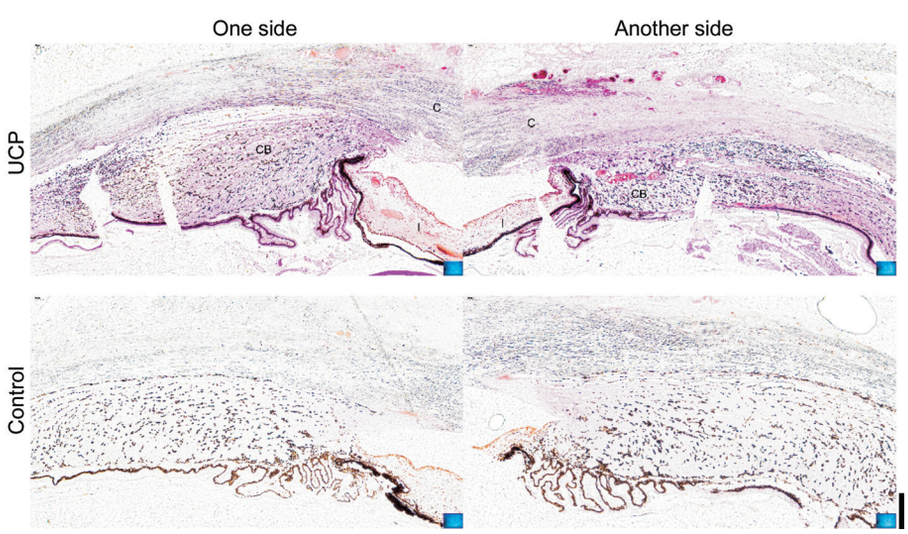


**Figure 5 Fuchsin anterior chamber perfusion staining** Fuchsin 1% anterior chamber perfusion revealed enhanced dye accumulation predominantly in the ciliary muscle interstices of UCP-treated eyes, contrasting with minimal staining observed in controls. UCP: Ultrasound cycloplasty; CB: Ciliary body; C: Cornea; I: Iris. Scale bar=300 μm.

complete success (defined as an IOP<21 mm Hg), regardless of glaucoma medications.

Our clinical and animal studies also revealed similar results regarding the IOP-lowering efficacy and with fewer side effects of UCP. In addition, changes in the structure of the anterior segment of the eyes upon UCP, relevant to its IOP-lowering effects, were evaluated. In our clinical study the UCP reduced the mean IOP from 39.08±14.75 mm Hg (baseline)

to 20.24±8.79 mm Hg (6mo post UCP treatment). Mean ACD increased from 2.10±0.91 mm (preoperative) to 2.20±0.88 mm at 1wk ($P$<0.05) post UCP treatment, corresponding to a mean ACD increase of 4.76%. Mean ACAn (angle between the posterior corneal surface and the anterior iris surface) increased from 5.81°±15.64° before the UCP procedure to 8.96°±16.99° 1wk post UCP treatment ($P$<0.05), corresponding to a mean ACAn increase of 54.22%. These changes in the anterior segments of eyes with ACG upon UCP procedure, such as ACD and ACAn, indicated that UCP could greatly lower IOP not only because of the reduction in AH production, but also through improving AH outflow, at least including TM, because increased ACD and ACAn stand for the opening of the ACAn, which is beneficial for AH outflow though the TM pathway, especially in patients with ACG[28].

However, some transient side effects of UCP were detected in the current study, such as slight hyperemia, dilated pupils, and anterior chamber flare, which disappeared one week after UCP treatment, except for the dilated pupils. Similarly, Almobarak *et al*[29] reported that the most common clinical complications of UCP observed in their study were anterior chamber reaction (18.5%), cataract progression (15.4%), and phthisis bulbi (3.1%, absolute glaucoma). Intraocular inflammation[24], hypotony with choroidal detachment[23], scleral ring congestion[30], peripheral cortical cataract[31] and scleral imprint[30] were relatively rare. Iris neovascularization and neurotrophic keratopathy have recently been reported to cause UCP-related side effects[32]. However, compared to cyclocryotherapy and trans-scleral diode laser photocoagulation, which utilize freezing and laser heating to destroy ciliary body tissue nonselectively, UCP is a more selective and precise approach[33]. High-intensity focused ultrasound induces focused, selective, and controlled thermal ablation effects on the ciliary body, regardless of tissue pigmentation and the damage to adjacent structures is limited[34]. UCP is an effective IOP-lowering treatment with good safety tolerance[35-38].

The same conclusion was supported by the results from the animal experiments, which showed significant IOP reduction from 23.10±1.96 to 9.67±2.85 mm Hg. Although a long-term study in monkeys with normal IOP treated with UCP showed a trend of IOP restoration, the degree of IOP reduction was obvious, up to more than 50%, from day 3 to day 21 after UCP. In our monkey study, transient inflammatory reactions were observed upon UCP, including slight hyperemia, dilated pupils, and anterior chamber flare, which disappeared one week after UCP treatment, except for the dilated pupils. Compared to patients, the anterior chamber inflammatory reaction was more severe in monkeys, which may be related to the fact that monkey eyes receive more sections[10] of UCP treatment.

Furthermore, there is evidence indicating that the good IOP lowering effects of UCP may be related to the increased AH outflow through uveoscleral pathways[17]. Mastropasqua *et al*[17] investigated the uveoscleral AH outflow pathways after UCP using anterior-segment optical coherence tomography (AS-OCT) and *in vivo* confocal microscopy. The AS-OCT results indicated that the mean intra-scleral hyporeflective space area (MIHSA) increased twofold and threefold in the UCP treated groups using 4 and 6 sections, respectively. *In vivo* confocal microscopy revealed that the mean density and area of the conjunctival microcysts increased in both groups. There was a significant relation between MIHSA increase and IOP lowering amplitude, $P$<0.01[17]. Interestingly, our UBM results showed a similar phenomenon; widened perichoroidal spaces were found in most UCP-treated patients.

However, the histological evidence for this is still lacking. Our experimental animal model results provide direct evidence of opening of the uveoscleral AH outflow pathway after UCP. H&E staining of the anterior segment paraffin sections showed widened ciliary muscle gaps, and SEM results showed more concentrated ciliary muscle fibers, which may provide space for the gaps among ciliary muscle fibers. This ciliary body phenotype is a typical open uveoscleral pathway, similar to the ciliary body form after long-term (one year) treatment with prostaglandin agonists[39]. Richter *et al*[39] investigated morphological changes in the anterior eye segments of cynomolgus monkeys topically treated with 0.03% bimatoprost, 0.03% sulprostone and an Prostagland in E2 Receptor Subtype 2 (EP2) agonist 0.01% AH13205 for 1y. They found that the biggest change in those monkeys' ciliary bodies treated with prostaglandin agonists was the significantly increased empty space found between muscle bundles in the anterior portion of the longitudinal and reticular ciliary muscles, indicating opened uveoscleral outflow routes and increased uveoscleral and conventional outflow[39].

Finally, the most direct evidence comes from the fuchsin anterior chamber perfusion staining. Stained tissues included the non-pigmented ciliary epithelium, sclera, and subconjunctival space of the UCP group, which are involved in the uveoscleral outflow route[40-41]. Meanwhile, only the TM and part of the ACAn in the control group were stained in light pink. This strong contrast directly demonstrates the open and closed states of the uveoscleral channel between the experimental and control groups after UCP treatment.

Interestingly, the non-pigmented ciliary epithelium in the monkey eye H&E slides of the UCP-treated group remained relatively intact, while these parameters improved the anterior angle and widened the ciliary muscle gaps, which was beneficial for increasing AH outflow[42-44] revealed that increased AH outflow through both the TM and uveoscleral

pathways plays a more important role in UCP. Aptel *et al*[22] investigated the non-pigmented ciliary epithelial structure of UCP-treated rabbits and found an involution process of ciliary destruction after UCP. From month 1 to month 6, short or absent ciliary processes with non-bilayered epithelium, non-functional cell coverage, and the absence of a deeper layer were observed[22]. In addition, another study from the same group on the histological sections of UCP-treated rabbit eyes harvested on day 28 post-treatment also showed coagulation necrosis, loss of the bilayered epithelium, and vascular depletion of the stroma during the ciliary processes[15]. These results differ from ours, possibly due to the different harvesting time points.

In conclusion, the relatively intact monkey non-pigmented ciliary epithelium after UCP revealed that UCP is a safe, noninvasive surgery that can efficiently lower IOP with or without the help of an additional medication assistant[45-47], especially for ACG. Increased AH outflow through both the TM and uveoscleral pathways plays a more important role in the IOP-lowering effects of UCP than previously thought.

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**REFERENCES**

1 Jayaram H, Kolko M, Friedman DS, *et al*. Glaucoma: now and beyond. *Lancet* 2023;402(10414):1788-1801.

2 Guglielmi P, Carradori S, Campestre C, *et al*. Novel therapies for glaucoma: a patent review (2013-2019). *Expert Opin Ther Pat* 2019; 29(10):769-780.

3 Park J, Rittiphairoj T, Wang X, *et al*. Device-modified trabeculectomy for glaucoma. *Cochrane Database Syst Rev* 2023;3(3): CD010472.

4 Bicket AK, Le JT, Azuara-Blanco A, *et al*. Minimally invasive glaucoma surgical techniques for open-angle glaucoma: an overview of cochrane systematic reviews and network meta-analysis. *JAMA Ophthalmol* 2021;139(9):983-989.

5 Lo J, Mehta K, Dhillon A, *et al*. Therapeutic strategies for glaucoma and optic neuropathies. *Mol Aspects Med* 2023;94:101219.

6 Obstbaum SA, Cioffi GA, Krieglstein GK, *et al*. Gold standard medical therapy for glaucoma: Defining the criteria identifying measures for an evidence-based analysis. *Clin Ther* 2004;26(12):2102-2120.

7 Cvenkel B, Kolko M. Current medical therapy and future trends in the management of glaucoma treatment. *J Ophthalmol* 2020;2020(1): 6138132.

8 Lewczuk K, Jabłońska J, Konopińska J, *et al*. Schlemm's canal: the outflow 'vessel'. *Acta Ophthalmol* 2022;100(4): e881-e890.

9 Sharif NA, Odani-Kawabata N, Lu FH, *et al*. FP and EP2 prostanoid receptor agonist drugs and aqueous humor outflow devices for treating ocular hypertension and glaucoma. *Exp Eye Res* 2023;229:109415.

10 Dastiridou AI, Katsanos A, Denis P, *et al*. Cyclodestructive procedures in glaucoma: a review of current and emerging options. *Adv Ther* 2018;35(12):2103-2127.

11 Mastropasqua R, Fasanella V, Mastropasqua A, *et al*. High-intensity focused ultrasound circular cyclocoagulation in glaucoma: a step forward for cyclodestruction *J Ophthalmol* 2017;2017:7136275.

12 Wang RX, Ding WJ, Jiang L, *et al*. A comparative study of ultrasound cycloplasty and endoscopic cyclophotocoagulation in the treatment of secondary glaucoma. *Sci Rep* 2023;13(1):23073.

13 Charrel T, Aptel F, Birer A, *et al*. Development of a miniaturized HIFU device for glaucoma treatment with conformal coagulation of the ciliary bodies. *Ultrasound Med Biol* 2011;37(5):742-754.

14 Giannaccare G, Sebastiani S, Campos EC. Ultrasound cyclo plasty in eyes with glaucoma. *JoVE* 2018(131): 56192.

15 Aptel F, Charrel T, Palazzi X, *et al*. Histologic effects of a new device for high-intensity focused ultrasound cyclocoagulation. *Invest Ophthalmol Vis Sci* 2010;51(10):5092.

16 Bolek B, Wylęgała A, Wylęgała E. Assessment of scleral and conjunctival thickness of the eye after ultrasound ciliary plasty. *J Ophthalmol* 2020;2020(1):9659014.

17 Mastropasqua R, Agnifili L, Fasanella V, *et al*. Uveo-scleral outflow pathways after ultrasonic cyclocoagulation in refractory glaucoma: an anterior segment optical coherence tomography and in vivo confocal study. *Br J Ophthalmol* 2016;100(12):1668-1675.

18 Lim KS. Ultrasound cycloplasty in glaucoma–mechanisms of action and their possible impact on intraocular pressure. *Eur Ophthalmic Rev* 2017;11(1):35.

19 Zheng SY, Wang DQ, Huang ZH, *et al*. The agreement of the nomogram tool and ultrasound biomicroscopy images in calculating ultrasound cycloplasty probe model in Chinese patients. *Ophthalmic Res* 2023;66(1):1191-1197.

20 Aptel F, Charrel T, Lafon C, *et al*. Miniaturized high-intensity focused ultrasound device in patients with glaucoma: a clinical pilot study. *Invest Ophthalmol Vis Sci* 2011;52(12):8747-8753.

21 Tan JK, Liu G, Zhu XJ, *et al*. Lentiviral vector-mediated expression of exoenzyme C3 transferase lowers intraocular pressure in monkeys. *Mol Ther* 2019;27(7):1327-1338.

22 Aptel F, Béglé A, Razavi A, *et al*. Short- and long-term effects on the ciliary body and the aqueous outflow pathways of high-intensity focused ultrasound cyclocoagulation. *Ultrasound Med Biol* 2014;40(9):2096-2106.

23 Almobarak FA, Alrubean A, Alsarhani WK, *et al*. Outcomes of ultrasound cyclo plasty in primary angle closure glaucoma. *J Glaucoma* 2023;32(5):407-413.

24 Figus M, Posarelli C, Nardi M, *et al*. Ultrasound cyclo plasty for treatment of surgery-Naïve open-angle glaucoma patients: a prospective, multicenter, 2-year follow-up trial. *J Clin Med* 2021;10(21):4982.

25 Giannaccare G, Vagge A, Sebastiani S, *et al*. Ultrasound cyclo-plasty in patients with glaucoma: 1-year results from a multicentre prospective study. *Ophthalmic Res* 2019;61(3):137-142.

26 Wu TH, Li JQ, Lu PR. Efficacy and safety of ultrasound cycloplasty for the treatment of glaucoma: a Meta-analysis. *Int J Ophthalmol* 2023;16(8):1317-1325.

27 Giannaccare G, Pellegrini M, Bernabei F, *et al*. A 2-year prospective multicenter study of ultrasound cyclo plasty for glaucoma. *Sci Rep* 2021;11(1):12647.

28 Xu L, Cao WF, Wang YX, *et al*. Anterior chamber depth and chamber angle and their associations with ocular and general parameters: the Beijing eye study. *Am J Ophthalmol* 2008;145(5):929-936.

29 Almobarak FA, Alrubean A, Alsarhani WK, *et al*. Ultrasound cyclo plasty in advanced glaucoma: Intermediate-term success, predictors for failure and complications. *Eur J Ophthalmol* 2024;34(6):1949-1956.

30 Zhou LF, Hu D, Lan J, *et al*. Efficacy and safety of single Ultrasound Cyclo-Plasty to treat refractory glaucoma: Results at 1 year. *Eur J Ophthalmol* 2022;32(1):268-274.

31 Luo JH, Liu Z, Zhao L, *et al*. Postoperative complicated peripheral cortical cataract after ultrasound cycloplasty: a case report. *BMC Ophthalmol* 2021;21(1):16.

32 Chen ZD, Wu YY, Yu MB. Iris neovascularization and neurotrophic keratopathy following ultrasound cycloplasty in refractory glaucoma: case series. *BMC Ophthalmol* 2024;24(1):188.

33 Wang T, Wang RX, Su Y, *et al*. Ultrasound cyclo plasty for the management of refractory glaucoma in Chinese patients: a before-after study. *Int Ophthalmol* 2021;41(2):549-558.

34 Posarelli C, Covello G, Bendinelli A, *et al*. High-intensity focused ultrasound procedure: The rise of a new noninvasive glaucoma procedure and its possible future applications. *Surv Ophthalmol* 2019;64(6):826-834.

35 Luo Q, Xue WW, Wang YL, *et al*. Ultrasound cycloplasty in Chinese glaucoma patients: results of a 6-month prospective clinical study. *Ophthalmic Res* 2022;65(4):466-473.

36 Paul C, Divya J, Sengupta S, *et al*. Efficacy and safety of ultrasound cycloplasty in Indian eyes with open-angle glaucoma. *Indian J Ophthalmol* 2022;70(12):4168-4171.

37 Morais Sarmento T, Figueiredo R, Garrido J, *et al*. Ultrasonic circular cyclocoagulation prospective safety and effectiveness study. *Int Ophthalmol* 2021;41(9):3047-3055.

38 Zhong H-M, Huang S-Y, Yao H-P, *et al*. Efficacy of ultrasound cyclo-plasty in patients with refractory glaucoma. *Int J Ophthalmol* 2025;18(3):420-423.

39 Richter M, Krauss AH, Woodward DF, *et al*. Morphological changes in the anterior eye segment after long-term treatment with different receptor selective prostaglandin agonists and a prostamide. *Invest Ophthalmol Vis Sci* 2003;44(10):4419-4426.

40 Costagliola C, Dell'Omo R, Agnifili L, *et al*. How many aqueous humor outflow pathways are there *Surv Ophthalmol* 2020;65(2):144-170.

41 Pederson JE, Gaasterland DE, MacLellan HM. Uveoscleral aqueous outflow in the rhesus monkey: importance of uveal reabsorption. *Invest Ophthalmol Vis Sci* 1977;16(11):1008-1007.

42 Murgoitio-Esandi J, Xu BY, Song BJ, *et al*. A mechanistic model of aqueous humor flow to study effects of angle closure on intraocular pressure. *Trans Vis Sci Tech* 2023;12(1):16.

43 Jonas JB, Jonas RA, Jonas SB, *et al*. Ciliary body size in chronic angle-closure glaucoma. *Sci Rep* 2023;13:16914.

44 Li HL, Yu S, Fan S, *et al*. Segmental uveoscleral outflow and its relationship with trabecular outflow in monkey eyes. *Invest Ophthalmol Vis Sci* 2025;66(4):78.

45 Rouland JF, Aptel F. Efficacy and safety of ultrasound cycloplasty for refractory glaucoma: a 3-year study. *J Glaucoma* 2021;30(5):428-435.

46 Wang RX, Li N, Chen XY. Ultrasound cyclo-plasty for moderate glaucoma: Eighteen-month results from a prospective study. *Front Med* 2022;9:1009273.

47 Chen D, Guo XJ, Luo SK, *et al*. Efficacy and safety of high-intensity focused ultrasound cyclo-plasty in glaucoma. *BMC Ophthalmol* 2022;22(1):401.