Precision Pulse Capsulotomy
Preclinical Safety and Performance of a New Capsulotomy Technology

David F. Chang, MD,1 Nick Mamalis, MD,2 Liliana Werner, MD, PhD2

Purpose: To assess the preclinical safety and performance of a new precision pulse capsulotomy (PPC) method.

Design: Human cadaver eye studies and surgical, slit-lamp, and histopathologic evaluation in a consecutive series of 20 live rabbits.

Participants: Human cadaver eyes and New Zealand white rabbits.

Methods: Precision pulse capsulotomy uses a highly focused, fast, multipulse, low-energy discharge to produce a perfectly round anterior capsulotomy instantaneously and simultaneously along all 360°. Capsulotomies are performed using a disposable handpiece with a soft collapsible tip and circular nitinol cutting element. Miyake-Apple imaging and scanning electron microscopy (SEM) of PPC were conducted in human cadaver eyes. Surgical, postoperative slit-lamp, and histopathologic assessments of PPC were performed in 20 live rabbits and were compared with manual continuous curvilinear capsulorrhexis (CCC) in the fellow eye. Anterior chamber (AC) thermocouple temperature measurements were evaluated in a subset of rabbit eyes.

Main Outcome Measures: Capsulotomy edge circularity, SEM morphologic features and zonular movement with PPC in human cadaver eyes. Anterior chamber temperature during PPC and grading of ocular inflammation, corneal endothelial damage, anterior capsular opacification (ACO), and posterior capsular opacification (PCO).

Results: Miyake-Apple imaging showed minimal zonular stress, and thermocouple measurements demonstrated negligible AC temperature changes during PPC. Precision pulse capsulotomy produced round, complete capsulotomies in all 20 rabbit eyes, leading to successful in-the-bag intraocular lens (IOL) implantation. Slit-lamp examinations at 3 days and 1, 2, and 4 weeks after surgery showed no significant differences between PPC and CCC in corneal edema, AC inflammatory reaction, capsular fibrosis, ACO, and PCO. Postmortem studies showed no difference in the corneal endothelium between PPC and CCC eyes. All IOLs were well centered in PPC eyes, and histopathologic analysis showed no greater inflammatory infiltrates.

Conclusions: Precision pulse capsulotomy is a new method to automate consistent creation of a perfectly circular anterior capsulotomy with a disposable handheld instrument that can be used in the normal phacoemulsification surgical sequence. Compared with CCC in fellow rabbit eyes, PPC was equally safe and showed no greater zonular stress compared with CCC in human cadaver eyes. Human cadaver eye SEM showed a much smoother capsulotomy edge compared to those produced by femtosecond laser. Ophthalmology 2015;1:1–10 © 2015 by the American Academy of Ophthalmology.

Continuous curvilinear capsulotomy (CCC) is one of the most important components of cataract surgery because of the numerous surgical and anatomic advantages it confers. The continuous edge facilitates hydrodissection, cortical aspiration, intraocular lens (IOL) implantation and fixation and renders the capsular bag more resistant to tearing during surgery.1,2 Circumferential anterior capsular overlap of the optic edge optimizes IOL centration, reduces posterior capsular opacification, decreases unwanted optical edge dysphotopsias, and may enhance predictability of the effective lens position.3–6 In contrast, radial anterior capsular tears increase the risk of surgical complications, reduce refractive accuracy, and may preclude using certain IOL designs.7,8

The ability to automate a perfectly circular capsulotomy of a consistently precise diameter has driven interest in and adoption of femtosecond laser-assisted cataract surgery.9–12 However, femtosecond laser-assisted cataract surgery necessitates significant capital and per-case costs, alters and slows the normal operative workflow, and cannot be used on every patient because of affordability or regulatory limitations. In addition, there is evidence that a capsulotomy created with the femtosecond laser may not resist tearing as well as the manual capsulorrhexis.13–15

We describe a new precision pulse capsulotomy (PPC) technology that is able to create a quick, precise circular capsulotomy using a disposable handheld instrument called the Zepto (Mynosys, Fremont, CA). The PPC Zepto device
is introduced during surgery in the conventional surgical sequence and potentially can be centered on the visual axis to produce a capsulotomy of a predetermined diameter.

Methods

Description of Precision Pulse Capsulotomy Device

Precision pulse capsulotomy is performed using a disposable handpiece and capsulotomy tip called the Zepto (Fig 1A) that is connected to a control console for operation (Fig 1B). The capsulotomy tip consists of a soft, transparent, silicone suction cup approximately 6 mm in diameter that houses a circular ring element made of the shape memory alloy nitinol. This nitinol ring element has been refined precisely at the micrometer scale to enable consistent and uniform 360° capsulotomies. The superelastic properties of nitinol allow the capsulotomy tip to be deformed mechanically into a narrower elongated shape for entry through a clear corneal incision. The ring can then re-expand automatically to its native circular shape within the anterior chamber (AC). The elongation of the capsulotomy tip is produced by the extension of a push rod, which then is retracted from the tip to allow it to reassume its original circular state.

The PPC handpiece and system were designed through extensive testing in rabbit eyes, porcine eyes, and in human cadaver eyes from donors in the 50- to 90-year age range. The PPC handpiece substitutes for capsulorrhexis forceps and is connected to a control console for operation (Fig 1B). The PPC methodology in a human cadaver eye is illustrated in Figure 2. Precision pulse capsulotomy is performed on the anterior capsule after open sky eye preparations. The morphologic features of the anterior capsulotomy edge produced by PPC in human cadaver eyes was examined using scanning electron microscopy. Precision pulse capsulotomy was performed after disinserting the iris tissue from cadaver eyes and centering the PPC device at the approximate center of the anterior capsule using suction delivered through the suction cup. An extendable and retractable push rod assists in device entry. The foot switch serves as to initiate PPC and also acts as an emergency stop.

Human Cadaver Eye Studies

Cadaver eyes were obtained from eye banks in the United States and were used within 72 hours of death for the Miyake-Apple imaging of zonular structures during PPC and for the analysis of PPC capsulotomy edge morphologic features using scanning electron microscopy. Precision pulse capsulotomy was performed after disinserting the iris tissue from cadaver eyes and centering the PPC device at the approximate center of the anterior capsule using the limbus as the circumferential boundary.

Zonular forces during performance of PPC were compared with those with manual CCC using Miyake-Apple imaging in paired human cadaver eyes. The eyes were prepared as previously described[6,7] and placed into an imaging system consisting of a head model, the underside of which contained a 5-megapixel Universal Serial Bus (USB) video camera. The dissected eye preparation was mounted into the modified eye socket of the head model, and video recordings of PPC or manual CCC were made from below to view the zonular structures during the performance of these 2 different capsulotomy methods.

The morphologic features of the anterior capsulotomy edge produced by PPC in human cadaver eyes was examined using scanning electron microscopy. Precision pulse capsulotomy was performed and video recordings of PPC or manual CCC were made from below to view the zonular structures during the performance of these 2 different capsulotomy methods.

The globe then was mounted into a glass vessel and submerged in 0.9% saline for hydrodissection, phacoemulsification, and cortical aspiration. A rim of capsule encompassing the capsulotomy opening was dissected free and placed in 2.0% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4, overnight at 4°C. The capsule specimens underwent dehydration using a graded ethanol series and were placed in between steel filter discs with the capsulotomy edge exposed. After processing in a critical point dryer, the specimens were gold-palladium sputtered and imaged using an Quanta 3D FEG scanning electron microscope (FEI, Hillsboro, OR) with the beam voltage set at 5 kV.

Figure 1. Photographs of the precision pulse capsulotomy (PPC) handpiece capsulotomy tip, handpiece, control console, and foot switch. A, View of the PPC capsulotomy tip from below. A circular ring made of the superelastic shape memory alloy nitinol is housed within a soft silicone housing that serves as a suction cup. An extendable and retractable push rod assists in device entry. B, View of the PPC handpiece, control console, and foot switch. The foot switch serves as to initiate PPC and also acts as an emergency stop.
Live Rabbit Studies

Precision pulse capsulotomy safety and performance during cataract surgery were assessed in a study of 20 New Zealand white rabbits 11 to 14 weeks of age. Animals were obtained from a United States Department of Agriculture-approved vendor (Western Oregon Rabbit Company, Philomath, OR) in accordance with the Animal Welfare Act. Rabbit studies complied with the Guide for the Care and Use of Laboratory Animals, as well as with guidelines set by the Association for Research in Vision and Ophthalmology. Rabbits received 3 doses of 1% cyclopentolate hydrochloride and 2.5% phenylephrine eye drops at 15-minute intervals. The rabbits were anesthetized with an intramuscular injection of ketamine hydrochloride (50 mg/kg) and xylazine (7 mg/kg) at 15-minute intervals. The rabbits were anesthetized with an intramuscular injection of ketamine hydrochloride (50 mg/kg) and xylazine (7 mg/kg) in a 7:1 mixture. One drop of topical proparacaine hydrochloride anesthetic and 1 drop of Povidone-iodine 5% were placed onto each eye before surgery. A side-port incision was made followed by injection of the ophthalmic vicsurgical device (Optivisc; Hoya, China Hills, CA). After placement of a 3.0-mm primary limbal incision, the PPC capsulotomy tip was inserted through this incision into the AC. After performing the anterior capsulotomy, the PPC device was removed from the eye. Hydrodissection was performed, followed by phacoemulsification and cortical aspiration. Each 500 ml of irrigation solution contained 1 ml epinephrine 1:1000 and 0.5 ml heparin (10 000 USP units/ml). iSert posterior chamber IOLs were implanted using the iSert Pre-loaded Lens Implantation System (Hoya). The fellow eye in each rabbit was treated identically except that a manual CCC was performed instead of PPC.

Because PPC uses electrical energy, intraocular temperatures were measured during device use. The surgical procedure otherwise was identical except that a thermocouple was inserted through the side-port incision into the AC in 6 of the 20 rabbits before initiating PPC. Continuous temperature measurements were made at 1 of 2 different locations inside the AC during the capsulotomy step (see Fig 4). At location A, the thermocouple tip was adjacent to the silicone side wall of the PPC device, and as close as possible to the nitinol ring. At location B, the thermocouple tip was positioned next to corneal endothelium located closest to the nitinol ring. The thermocouple was removed before phacoemulsification and IOL implantation.

All study eyes (PPC and CCC) were subjected to gross examination on postoperative day 1 and assessed for infection, inflammation, hemorrhage, and wound leak. Dilated slit-lamp examinations were conducted on postoperative day 3 and at 1, 2, and 4 weeks. Conjunctival injection, corneal edema, aqueous cells and flare, iris vasculature, posterior synechiae, IOL centration, and IOL inflammatory deposits were noted. Anterior and posterior capsule opacification were graded on a 0-to-4 scale at each examination. At the end of the 4-week study period, the rabbits were euthanized and the globes were harvested and fixed in 10% neutral buffered formalin. All globes were bisected coronally just anterior to the equator. Gross examination and photography from the posterior aspect (Miyake-Apple view) were performed. Tissue sections were obtained from all eyes and stained with hematoxylin and eosin for light microscopic examination of inflammatory cells, necrosis, and cell vaculization in various ocular structures.

Histologic examination was performed to compare morphologic damage to the corneal endothelium after PPC and CCC. After clinical examination on postoperative day 3, 6 study rabbits that underwent PPC and manual CCC in their fellow eyes were euthanized. The 12 corneas with a rim of surrounding sclera were removed from the harvested globes for study. The cornea buttons were placed endothelial side up and stained using a modification of a method by Spence and Peyman consisting of immersion in Trypan blue 0.25% and Alizarin red 1%. Central corneal buttons 8 mm in diameter were punched out using a trephine, and the stained specimens were placed on a microscopic slide,
endothelium side up, for microscopic evaluation. Photomicrographs of the endothelium were obtained using light microscopy to assess endothelial damage. Image J software (National Institute of Health, Bethesda, MD) was used to calculate and compare the areas of endothelial cell damage in PPC versus CCC eyes.

Results

Human Cadaver Eye Studies

Representative examples of anterior capsulotomies resulting from PPC in human cadaver eyes are shown in Figure 5. In each case, the capsulotomy openings were perfectly round, were free of tags, and exhibited a well-defined, clean edge. Precision pulse capsulotomy created capsulotomies measuring in the range of 5.1 to 5.3 mm in diameter.

Miyake-Apple video imaging comparing PPC and manual capsulorrhexis in paired human cadaver eyes demonstrated no greater zonular movement with PPC. Insignificant movement of the zonules was observed throughout the entire PPC procedure, including during suction application, capsulotomy creation, suction reversal, and detachment of the capsulotomy device from the lens (Fig 6). Overall, Miyake-Apple imaging showed that the suction-activated PPC device seemed to stabilize the lens during performance of the capsulotomy.

Scanning electron microscopy imaging showed that the PPC capsulotomy edge morphologic features are unique and differ from those observed with both manual capsulorrhexis and femtosecond laser capsulotomy (Fig 7A). Morphologic evidence demonstrated that the instantaneous vapor expansion and cleaving of the capsule membrane anneals the collagen and tightens the collagen fibril structure comprising the PPC cut edge (Fig 7B). In addition, there was a circumferential microscopic eversion of the capsulotomy edge resulting in the presentation of the smooth underside of the anterior capsule adjacent to the cut (Fig 7B, C). This intact, defect-free capsule underside is only approximately 20 μm wide and becomes the actual rounded functional or working edge of the capsulotomy opening during surgery.

Rabbit Eye Studies

Precision pulse capsulotomy and manual CCC were completed successfully in fellow eyes of 20 rabbits. The device was inserted
and subsequently removed through a 3.0-mm incision. All PPC procedures resulted in a complete tag-free capsulotomy with the capsule button extracted simultaneously by the PPC device (Table 1). All PPC eyes successfully underwent hydrodissection, phacoemulsification, cortical aspiration, and IOL implantation in the capsular bag. The geometry of PPC capsulotomies was consistently rounder than those obtained using manual CCC as judged by slit-lamp observation (Fig 8).

Continuous thermocouple temperature measurements during PPC showed negligible, transient temperature changes at both positions A and B within the AC (Fig 4; Table 2). The measured mean peak temperature rise at location A was only 2°C. The mean measured peak temperature rise at location B was barely 1°C. The duration of these minor temperature changes lasted only several seconds.

In the subset of 6 rabbits (6 PPC eyes and 6 fellow CCC eyes) harvested on postoperative day 3 and evaluated with corneal endothelial cell staining, there was no statistical difference in the amount of morphologic corneal endothelial damage between eyes undergoing PPC or manual CCC (Table 1). The postoperative course was otherwise unremarkable for all PPC and manual CCC study eyes (Table 1). Gross examination on postoperative day 1 noted corneal edema only at the incision site, with no difference between PPC and manual CCC eyes. Postoperative day 3 findings also were similar for both groups, and included statistically comparable degrees of aqueous cells, iris hyperemia, AC fibrin formation, and corneal edema that was predominantly near the incision. Clinical corneal edema on postoperative day 3 findings were also similar between both groups, as analyzed both by the corneal opacity score and by multiplying corneal opacity by opacity extent. There were also no postoperative day 3 differences in terms of aqueous cells, iris hyperemia, and fibrin score. Each of these postoperative day 3 findings resolved in all eyes (PPC and CCC) by the week 2 examination.

The diameter of rabbit capsulotomies tends to increase after surgery because of the higher elasticity of the rabbit anterior capsule. No difference in capsulotomy expansion was noted between eyes that underwent PPC or manual CCC. Rabbit eyes also provide an accelerated model of anterior capsular opacification and posterior capsular opacification (PCO). There were no differences between the 2 groups in terms of PCO, proliferative lens epithelial cell pearls anterior to the IOL, posterior synechiae, or capsulotomy edge fibrosis at the week 4 examination.

Postmortem examination of all globes at 4 weeks showed that all IOLs were fixated symmetrically within the capsular bag (Fig 7C, D). There were no differences between the 2 groups in terms of central PCO, peripheral PCO, Soemmerring’s ring formation, anterior capsular opacification, IOL coverage by the capsulotomy, or IOL decentration (Table 1).

Microscopic histopathologic examination of tissue sections from eyes of both PPC and CCC groups at 4 weeks showed no significant difference in Soemmerring’s ring formation, PCO, anterior cortical proliferation, and anterior fibrous metaplasia. There was no evidence of toxicity or excessive inflammation in any of the PPC or manual CCC eyes.

Discussion

The ideal anterior capsulotomy would be continuous, circular, centered on the visual axis, maximally resistant to
tearing, and of a precise diameter that circumferentially overlaps the IOL optic edge. An inexpensive automated technology that could create such a capsulotomy consistently and reproducibly as an integrated surgical step would be attractive to most surgeons. Ideally, it would improve rather than decrease surgical efficiency and the cost would be low enough so that it could be used on all patients. Femtosecond laser-assisted cataract surgery is appealing in part for its ability to automate creation of a perfectly circular capsulotomy. However, the technology is costly, requires supplemental patient payment, and disrupts the normal operative workflow. In addition, several published studies have raised concerns that the femtosecond laser capsulotomy is less resistant to tearing compared with a manual capsulorrhexis.9–11 The precision pulse capsulotomy technology described and evaluated herein was developed to provide a potentially superior and less expensive method to automate creation of a perfectly circular capsulotomy.

Testing in human cadaver eyes as well as in live rabbit eyes showed that the precision pulse technology is able to create a perfectly circular capsulotomy without tags consistently and instantaneously. The version of the PPC device used in these studies was designed to fit through a 3.0-mm corneal incision. A newer version of the device under development should fit through a 2.2-mm incision.
Potential safety concerns were studied before clinical application in a variety of ways. Miyake-Apple imaging in human cadaver eyes provided visual evidence that this capsulotomy method caused no greater zonular traction than with a manual capsulorrhexis. As measured with thermocouple probes, the local peak temperature rise in the area just adjacent to the nitinol ring, and near the overlying corneal endothelium, was insignificant and returned to baseline within 2 to 4 seconds. Such momentary, minute temperature increases are unlikely to cause endothelial cell or collateral tissue damage. This temperature safety is likely because of the very fast and focused millisecond delivery of energy for capsulotomy. In addition, the silicone suction cup that surrounds the nitinol ring is an excellent heat insulator and provides additional shielding.

In a companion article, we present data from 44 paired human cadaver eyes demonstrating that the PPC edge is consistently more resistant to tearing compared with both the manual capsulorrhexis edge and the femtosecond laser capsulotomy edge. Unlike other capsulotomy techniques that involve tissue cauterization, PPC does not cause tissue burning, which has been demonstrated to result in a less extensible capsulotomy opening. Scanning electron microscopy analysis of the PPC capsulotomy edge showed unique characteristics different from the capsule edge produced by either manual capsulorrhexis or by the femtosecond laser. The annealing of collagen at the cut edge and the use of suction to induce tensile stress in the capsule under the nitinol element during PPC create a rounded functional edge consisting of 15 to 20 μm of...
In conclusion, a novel PPC technology performed using a disposable handpiece has been developed that can create a precisely sized, circular capsulotomy as an integrated step during conventional phacoemulsification. This technology may prove able to automate the capsulotomy step and produce a stronger capsulotomy edge, without the higher costs, longer procedural time, and the logistical challenges of using a femtosecond laser.
References


Footnotes and Financial Disclosures

Originally received: August 27, 2015.
Final revision: October 3, 2015.
Accepted: October 7, 2015.
Available online: • • • . Manuscript no. 2015-1481.

1 Altos Eye Physicians, Los Altos, California.
2 John A. Moran Eye Center, University of Utah, Salt Lake City, Utah.


Financial Disclosure(s):
The author(s) have made the following disclosure(s): D.F.C.: Consultant - Mynosys; LensAR: AMO
L.W.: Financial support - AMO; AcuFocus; Alcon; Bausch & Lomb; Calhoun Vision; ClarVista Medical; Genisphere; Hoya; LensGen; Mynosys; Omega; PowerVision; Sharklet; Advisory board - PowerVision

The research sponsor (Mynosys Cellular Devices Inc., Fremont, CA) participated in the design of the study.

Author Contributions:
Conception and design: Chang, Mamalis, Werner
Analysis and interpretation: Chang, Mamalis, Werner
Data collection: Chang, Mamalis, Werner
Obtained funding: none
Overall responsibility: Chang, Mamalis, Werner

Abbreviations and Acronyms:
AC = anterior chamber; ACO = anterior capsular opacification; CCC = continuous curvilinear capsulorhexis; IOL = intraocular lens; PPC = posterior capsular opacification; PPC = precision pulse capsulotomy; SEM = scanning electron microscopy.

Correspondence:
David F. Chang, MD, Altos Eye Physicians, 762 Altos Oaks Drive, Los Altos, CA 94024. E-mail: dceye@earthlink.net.