Title: Preclinical imaging of iridocorneal angle and fundus using a modified integrated flexible handheld probe

Author(s): Hong, Jeemond Xun Jie; Shinoj, Vengalathunadakal K.; Murukeshan, Vadakke Matham; Baskaran, Mani; Aung, Tin


Date: 2017

URL: http://hdl.handle.net/10220/45613

Rights: © 2017 SPIE. This paper was published in Journal of Medical Imaging and is made available as an electronic reprint (preprint) with permission of SPIE. The published version is available at: [http://dx.doi.org/10.1117/1.JMI.4.2.026001]. One print or electronic copy may be made for personal use only. Systematic or multiple reproduction, distribution to multiple locations via electronic or other means, duplication of any material in this paper for a fee or for commercial purposes, or modification of the content of the paper is prohibited and is subject to penalties under law.
Preclinical imaging of iridocorneal angle and fundus using a modified integrated flexible handheld probe

Xun Jie Jeasmond Hong
Vengalathunadakal K. Shinoj
Vadakke Matham Murukeshan
Mani Baskaran
Tin Aung
Preclinical imaging of iridocorneal angle and fundus using a modified integrated flexible handheld probe

Xun Jie Jeesmond Hong,a† Vengalathunadakal K. Shinoj,a Vadakke Matham Murukeshana,b† Mani Baskaran,b,c and Tin Aungb,c,d

aNanyang Technological University, Centre for Optical and Laser Engineering, School of Mechanical and Aerospace Engineering, Singapore
bDuke-NUS Medicine School, EYE-ACP, Singapore
cSingapore Eye Research Institute and Singapore National Eye Centre, Singapore
dYong Loo Lin School of Medicine, Department of Ophthalmology, Singapore

Abstract. A flexible handheld imaging probe consisting of a 3 mm × 3 mm charge-coupled device camera, light-emitting diode light sources, and near-infrared laser source is designed and developed. The imaging probe is designed with specifications to capture the iridocorneal angle images and posterior segment images. Light propagation from the anterior chamber of the eye to the exterior is considered analytically using Snell’s law. Imaging of the iridocorneal angle region and fundus is performed on ex vivo porcine samples and subsequently on small laboratory animals, such as the New Zealand white rabbit and nonhuman primate, in vivo. The integrated flexible handheld probe demonstrates high repeatability in iridocorneal angle and fundus documentation. The proposed concept and methodology are expected to find potential application in the diagnosis, prognosis, and management of glaucoma. © 2017 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.4.2.026001]

Keywords: ophthalmology; medical imaging; imaging systems; iridocorneal angle imaging; fundus imaging.

1 Introduction

Glaucoma is a group of diseases with characteristic optic nerve damage, resulting in the irreversible loss of vision. Most, but not all, of these diseases are characterized by an increase in intraocular pressure. Based on a global study on visual impairment, glaucoma is one of the leading causes of blindness, second only to cataracts. In 2010, the number of people affected by angle-closure glaucoma is one of the leading causes of blindness, second only to cataracts. In 2010, the number of people affected by angle-closure and open-angle glaucoma was estimated to be 60.5 million. This number is expected to increase by about 30% to 79.6 million in 2020. The different clinical subtypes of glaucoma also show specific geographical distributions. While those of African derivation are more susceptible to open-angle glaucoma, primary angle-closure glaucoma is more prevalent in Asian countries, such as China and India.

To determine whether a patient is affected with glaucoma or to monitor the disease progression, it is necessary to undergo a series of tests. The major objectives of these tests are (i) the measurement of intraocular pressure of the eye, (ii) assessment of possible damage of the optic nerve at the back of the eye, (iii) mapping of the complete field of vision, (iv) determination of corneal thickness, and (v) assessment of the drainage system to check for fluid in the anterior chamber of the eye. Unfortunately, the signs and symptoms associated with glaucoma are inconsistent among the various clinical subtypes and may not even be presented until permanent damage has occurred. The most indicative clinical hallmarks of glaucoma are abnormalities in the aqueous outflow system and optic nerve. While a wide angle allows sufficient drainage of aqueous humor through the trabecular meshwork (TM), a narrow angle obstructs the flow of the aqueous humor and can eventually lead to angle-closure glaucoma. On the other hand, stereo images of the optic nerve provide important information with regards to the cup to disc ratio, shape, and color of the optic nerve. The documentation of the iridocorneal angle region and optic nerve are, therefore, critical and necessary in the evaluation and assessment of glaucoma.

Gonioscopy, despite being the current gold standard in the diagnosis and management of glaucoma, is a subjective method. The documentation of the iridocorneal angle region by gonioscopy is through various grading procedures. Its main drawbacks include physician compliance and patient discomfort. Interpretations of gonioscopic images require expertise and are subjected to considerable disagreement between clinicians and vision researchers. In addition, this procedure is time-consuming and cumbersome. An earlier study revealed that gonioscopy was not performed on 50% of glaucoma patients in clinical examinations. On the other hand, RetCam is a fundus camera system originally designed to capture retina images for the diagnosis and monitoring of posterior segment diseases. With proper modifications, it can be used to document the anterior chamber angle. However, imaging of the iridocorneal angle region and fundus with RetCam requires a longer time and is costly. Moreover, the supine positioning of the patients in RetCam might cause an artifactual widening of the anterior chamber angle, resulting in underestimated measurements.

Our group has worked on many optical instrumentation projects for biomedical imaging applications. We have recently demonstrated a miniaturized integrated charge-coupled device (CCD) camera and light-emitting diode (LED) light probe imaging system to image and evaluate the iridocorneal angle of the porcine eye. This paper in this context discusses the modified probe system which can record, capture, and display images...
of the iridocorneal angle region and fundus using visible and near-infrared sources. Photographic techniques allow clinicians and vision researchers to document and track disease progression and treatment response over time. The imaging efficiency of this dual functionality imaging system is validated by capturing digital images of the porcine eye, with follow-up preliminary trials on animal models, indicating promising results. It is envisaged that this imaging system can enable accurate diagnostic procedures of glaucoma.

2 Methods

2.1 Preparation of Porcine Samples

The porcine eye is a suitable ex vivo animal model due to its high morphological similarities to that of the human eye. Furthermore, it is a validated animal model of glaucoma and is used in neuroretinal studies because of its similar retina structure to the human retina. Randomly selected eyes from five pigs (Sus scrofa domestica) were enucleated at the local abattoir and imaged within 4 h. To maintain its "freshness," the enucleated eyes were transported on ice and kept until the investigation started. The conjunctiva, lacrimal gland, as well as other extracocular tissues, were removed before fixing the eyes onto a custom eye holder.

2.2 Preparation of New Zealand White Rabbit and Macaca fascicularis

The New Zealand white rabbit (Oryctolagus cuniculus) was chosen for this study because it is a naturally occurring glaucoma model and is another naturally occurring glaucoma model used in this study due to its high homology and close phylogeny with humans. Their optic nerve and retinal anatomy are almost identical to that of human. The in vivo and ex vivo animal models have continuous endothelial lining at the aqueous outflow channels, similar to those in human. They are therefore validated models in this study.

Imaging of the New Zealand white rabbit and nonhuman primate was conducted at Singapore Eye Research Institute (SERI), in accordance with the guidelines of the National Advisory Committee for Laboratory Animal Research in Singapore. The New Zealand white rabbit was intramuscularly anesthetized with xylazine (10 mg/kg) and ketamine hydrochloride (50 mg/kg) whereas the nonhuman primate was anesthetized with medetomidine (0.02 mg/kg) and ketamine hydrochloride (10 mg/kg).

2.3 Imaging System

The distal end of the imaging probe has a diameter of 26 mm. It houses a 3 mm × 3 mm CCD video camera (IntroSpicio™ 115, Medigus Ltd., Israel) and is surrounded by two white-light LEDs, one near-infrared LED, and a 808-nm near-infrared diode laser source with optical output power of 140 mW (LuxX 808, Omicron Laserage, Rodgau, Germany). The CCD has a pixel size of 2.95 μm (horizontal) × 1.90 μm (vertical) and has 291,000 effective numbers of pixels (500 longitudinal × 582 lateral). It has a frame rate of 30 frames per second, a field of view (FOV) of 140 deg, depth of field of 5 to 100 mm, and a working distance of 20 mm. Each white-light LED has a viewing angle of 20 deg and a maximum luminous intensity of 7000 mcd. On the other hand, the near-infrared LED has a viewing angle of 20 deg, 940-nm peak emission wavelength, and a maximum radiant intensity of 30 nW/sr. The light sources are arranged in a circular ring array with a radius of 5.5 mm. The illumination conduits have internal diameters of 5 mm and are drilled at an angle of 71 deg with respect to the illumination plane array, for sufficient illumination across the entire FOV. The design is based on a Lambertian approach for isotropic luminescence. The design equations and formulas are adopted and derived geometrically from the design equations for a circular ring array of four LEDs at 0-deg illumination. A potentiometer is employed to control the brightness of the LEDs. The probe is coupled to a video processing unit, which is in turn linked to a personal computer for display and storage. The design of this imaging probe fulfills the safety directions recommended by the International Commission on Nonionizing Radiation Protection. Evaluation of retinal hazard is not required since the white-light LEDs have luminescence intensity lower than the threshold of 10,000 candela/m². For near-infrared imaging, the exposure limit falls well within the maximum permissible exposure limits for eye considering the wavelength, power, and exposure time needed for image acquisition.

2.4 Snell’s Law and Imaging Method

Snell’s law states that when light travels from a medium of higher optical density to a medium of lower optical density, it will bend or refract away from the normal. The phenomenon of total internal reflection (TIR) has to be taken into account when considering light transmission from the iridocorneal angle region, through the cornea, to the outside medium. Under normal conditions, light from the iridocorneal angle region is incident onto the tear-air interface at an angle smaller than the critical angle, and hence all of it will be reflected. A schematic illustration of light transmission from iridocorneal angle to air is shown in Fig. 1.

The micro-CCD camera is positioned precisely at the center, so the imaging axis coincides with the central axis. A thin layer of ophthalmic coupling gel (Vidisic Gel, Bausch & Lomb GmbH, Berlin, Germany) is applied onto the cornea. The probe is able to capture the anterior and posterior chambers of the eye when placed at the limbus or central cornea for iridocorneal angle imaging and fundus imaging, respectively. For iridocorneal angle imaging, the imaging probe is positioned at the corneal limbus to image the angle in the opposite quadrant. The
imaging schemes for iridocorneal angle imaging and fundus imaging are illustrated in Figs. 2(a) and 2(b), respectively.

3 Results and Discussion

Since the direct view of the iridocorneal angle is obstructed by the scleral overlap, the imaging probe is positioned at the limbal region to image the opposite iridocorneal angle, as illustrated in Fig. 1(a). TIR is avoided by altering the refractive index of the medium outside the cornea. Vidisc gel has a refractive index of about 1.33, very close to that of the cornea and aqueous humor. Optical distortion as a result of the corneal curvature is therefore reduced. Image acquisition is possible in single frame mode or fast kinetics mode. Since the camera has an FOV of 140 deg, only one image has to be taken from each quadrant, for a complete view of the iridocorneal angle region. The imaging probe can visualize the anterior chamber structures in a manner similar to direct gonioscopy, making interpretation easy. All the ex vivo and in vivo eyes had anatomically open angles. Figure 3 shows representative images of the iridocorneal angle in a porcine sample, a New Zealand white rabbit, and a nonhuman primate. In contrast to the porcine sample and nonhuman primate eye, which are heavily pigmented, the New Zealand white rabbit has a genetic deviation known as albinism. Nonetheless, normal iris processes can be seen reaching the scleral spur in all three images, indicating open angles. The use of white-light illumination causes constriction of pupils in live samples, thereby inducing an "open angle." This was, however, not a cause for concern with the ex vivo porcine samples since they will not have any change regardless of the lighting conditions. A dark-room provocation test was conducted using near-infrared sources to elicit primary angle closure. Figures 4(a) and 4(b) show the superior quadrant of the New Zealand white rabbit using white-light LEDs and near-infrared sources, respectively. The iridocorneal angle of the New Zealand white rabbit was not occluded in both cases.

Fundus imaging with the handheld probe is similar to direct ophthalmoscopy. It is based on the principle of reversibility of light. The pupil functions as an entrance for the illuminating LEDs and an exit for the imaging light rays. The retina and optic disc can be imaged directly enabling the clinicians and vision researchers to examine the shape and color of the optic nerve. Figure 5 shows fundus images of the porcine sample and New Zealand white rabbit. The arteries are relatively pale and...
thin, while the veins are relatively dark red and large. Interfering reflections and corneal reflection along the optical axis are significantly reduced since the trajectory of the illumination beams and observation beam are separated as shown in Fig. 5. The quality of the image may be degraded by media opacities. This problem can be overcome by increasing the illumination. It should be noted that there will be increased discomfort because the natural defense mechanisms of eyes, such as blinking, eye movements, glare avoidance, and squinting, are compromised during image acquisition.

With no all-round, foolproof concept and methodology for imaging angles, clinicians tend to use an individualized approach for the assessment of glaucoma. For example, some clinicians use the anterior segment optical coherence tomography (AS-OCT) as a first-pass method for detecting eyes with a narrow angle, as well as obtaining quantitative information about the depth of the angle before proceeding to gonioscopy. Those with the technical capabilities choose to perform gonioscopy on all glaucoma patients since it is the fundamental part of an eye examination. In EyeCam and RetCam assessments, the imaging of the iridocorneal angle region and fundus takes about 5 to 10 min and 1 min per eye, respectively, and requires change of distal end optics. Furthermore, the supine positioning of patients results in artificial widening of the anterior chamber angle, resulting in underestimated readings. Skilled and experienced operators are required, and the images obtained are similar to what is seen during gonioscopy. On the other hand, iridocorneal angle region and fundus imaging with the dual functionality imaging probe take less than 2 min per eye. Unlike the EyeCam/RetCam assessment, examination of the iridocorneal angle region and fundus with the imaging probe does not require any change in the distal end optics. The upright positioning of the patients allows the images to be captured in the most natural and dynamic state. Operation of the imaging system requires minimal expertise, and the images obtained are also similar to what is seen in gonioscopy. Critical anatomical structures of the aqueous outflow system, such as the iris root, ciliary body band, TM, and scleral spur, can be identified in a normal eye. The dual functionality imaging probe has variable resolution at different working distances. The working distances at the iridocorneal angle region and fundus are ~10 and 20 mm, respectively. Assuming uniform optical density in the anterior and posterior chambers, the imaging probe has resolutions of 10.08 lp/mm (~49.61 μm) at the iridocorneal angle region and 5.04 lp/mm (~99.21 μm) at the fundus. Photographic documentation allows observation of pathological changes in the iridocorneal angle region and fundus over time and can be used as patient education tools to help patients better understand their conditions in clinical settings. The proposed imaging probe is able to differentiate an open angle from a closed angle. It is also able to detect pathological conditions, such as peripheral anterior synchiae, hence allowing proper classification and appropriate management (see Appendix). Compression artifacts are circumvented by fluid-based optical coupling. The imaging system is portable and can be attached to any workstation or even a slit-lamp, installed with the interfacing software. Table 1 shows a comparison of imaging systems in clinical ophthalmology and the dual functionality imaging probe described in the paper.

4 Conclusion

A flexible ocular imaging probe to record, capture, and display images of the iridocorneal angle region and fundus is developed and illustrated. The imaging capability of the developed probe is demonstrated using ex vivo porcine samples and subsequently on naturally occurring glaucoma models, such as the New Zealand white rabbit and M. fascicularis, in vivo. The imaging system is able to give good quality digital images of the iridocorneal angle region and fundus with high repeatability and reproducibility. Not only does it reduce image acquisition time and patient discomfort, it is also a cheaper alternative to conventional photographic methods, such as gonioscopy and RetCam. The use of near-infrared sources for dark-room provocative test enables a predictive and objective evaluation for detecting iridocorneal angle closure. One of the future work directions is to extend its application to the surgical management and follow-up procedures of microinvasive glaucoma surgeries and goniosynechiolysis.

Appendix: Inducing High Intraocular Pressure in Ex Vivo Porcine Sample

Figure 8 shows images of the iridocorneal angle captured with the flexible handheld probe. Even though the porcine eye is heavily pigmented, it can be seen from Fig. 8(a) that the normal

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Fundus imaging</th>
<th>Iridocorneal angle imaging</th>
<th>Anatomical structures (anterior chamber)</th>
<th>Operator requirement</th>
<th>Patient position</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonioscopy</td>
<td>No</td>
<td>Yes</td>
<td>Easy identification</td>
<td>Skilled, contact</td>
<td>Upright</td>
<td>Low</td>
</tr>
<tr>
<td>AS-OCT</td>
<td>No</td>
<td>Yes</td>
<td>Difficult</td>
<td>Simple, noncontact</td>
<td>Upright</td>
<td>High</td>
</tr>
<tr>
<td>RetCam/EyeCam</td>
<td>No</td>
<td>Yes</td>
<td>Easy identification</td>
<td>Skilled, contact</td>
<td>Supine</td>
<td>High</td>
</tr>
<tr>
<td>Imaging probe in paper</td>
<td>Yes</td>
<td>Yes</td>
<td>Easy identification</td>
<td>Simple, contact</td>
<td>Upright</td>
<td>Low</td>
</tr>
</tbody>
</table>
iris processes are reaching toward the scleral spur. This indicates an open angle. In Fig. 6(c), a state of high intraocular pressure was induced in the ex vivo samples by deliberately injecting fluids into the vitreous chamber. The injection was done via a 29-gauge needle syringe. The increase in pressure caused the iris to close up toward the cornea, narrowing and occluding the iridocorneal angle. Figures 6(b) and 6(d) are indentation examinations in monitoring progression of early glaucoma damage, ex vivo.

**Fig. 6** Images acquired using the integrated flexible handheld probe. (a) An open angle where the iris processes are seen reaching toward the scleral spur. (b) The indentation examination of the same eye where the iris is flattened as the cornea is indented. (c) A closed angle of the same eye after deliberately injecting fluids into the vitreous chamber. The increase in pressure caused the iris to close up toward the cornea, narrowing and occluding the iridocorneal angle. (d) The indentation examination of the eye after injection. Part of the iris root is adhered to the cornea.

**Disclosures**

The authors have no relevant financial interests in the paper and no other potential conflicts of interest to disclose.

**Acknowledgments**

This work was supported in part by the National Research Foundation Proof-of-Concept under Grant 002040 and the Nanyang Technological University and SERI Research Collaboration Agreement under Grant 16/144. The authors also acknowledge the financial support toward research manpower and facilities provided at the Center for Optical and Laser Engineering, NTU.

**References**


Xun Jie JeesModule Hong received his BEng (hons) degree in bioengineering from Nanyang Technological University (NTU), School of Chemical and Biomedical Engineering in 2013. He is currently a PhD candidate and a project officer at the Center of Optical and Laser Engineering (COLE) at the same university. His current research interests include biomedical optics, optoelectronic systems, and bioinstrumentation.

Vengalathunadakal K. Shinoj received his PhD from NTU, Singapore, in 2012. His research focuses on design and development of an improved imaging probe for ocular imaging targeting acute-closure glaucoma diagnosis. His research findings have been published in many internationally recognized peer-reviewed journals and presented in various prestigious international conferences.

Vadakke Matham Murukeshan is an associate professor at the School of Mechanical and Aerospace Engineering and a deputy director of COLE, NTU. His main research interests are biomedical optics, nanoscale optics, and applied optics for metrology. He has published over 250 research articles in leading journals and conference proceedings and has 6 patents and 8 innovations disclosures. He is a fellow of the Institute of Physics and a member of SPIE.

Mani Baskaran is a clinician scientist at Singapore Eye Research Institute and an assistant professor at the Office of Clinical Sciences, Duke-NUS graduate Medical School, Singapore. His current research interests include the imaging, diagnosis, and management of angle closure in Asia and the development of innovative devices and software algorithms in anterior segment imaging. He has published more than 110 international publications and 8 book chapters and has 6 copatents in the field of glaucoma.

Tin Aung is a clinician scientist with clinical practice focusing on glaucoma and research interests in angle closure glaucoma and glaucoma genetics. He is the deputy medical director at Singapore National Eye Center, a senior consultant and head of the glaucoma department, and a professor in the Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. He is currently the president of the World Glaucoma Association.