Review Article

Taiwan J Ophthalmol 2022;12:409-414

Access this article online

Quick Response Code:

Website:
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DOI:
10.4103/tjo.tjo_41_21

Non-optical coherence tomography modalities for assessment of angle closure

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Abstract:

Primary angle closure glaucoma is a leading cause of irreversible blindness, particularly in Asia. Its pathophysiology is based in the closure of the anterior chamber angle (ACA). In addition to gonioscopy (current reference standard), in the past decade, anterior segment optical coherence tomography (AS-OCT) has been incorporated in routine ophthalmic practice to help assess the configuration of the ACA. Especially in nonspecialist ophthalmology practice, gonioscopy may be less frequently performed and AS-OCT may not be available, leading to the need of other anterior segment evaluation methods. Evaluating the anterior chamber depth (ACD) has long been recognized as screening tool for primary angle-closure glaucoma. It can be measured with several devices, such as Scheimpflug photography and the scanning peripheral ACD analyzer. It can also be estimated with the oblique flashlight test and van Herick technique (limbal ACD assessment). More recently, goniophotographic systems have been developed to produce images of the ACA similar to those seen with manual gonioscopy. NGS-1 automated gonioscope (NIDEK Co, Gamagori, Japan) and the RetCam (Natus Medical Incorporated, Pleasanton, CA) are commercially available. However, NGS-1 is the only one with a specialized software for ACA imaging. Several prototype devices are currently being developed, such as the GonioPEN and axicon lens assisted gonioscopy. This article aims to review different modalities of ACA assessment, beyond AS-OCT, and compare their relative advantages and disadvantages.

Keywords:

Angle closure glaucoma, anterior chamber depth, imaging, optical coherence tomography, screening

Introduction

Primary angle-closure glaucoma is a leading cause of irreversible blindness, particularly in Asia.[1] Its pathophysiology is based in the closure of the anterior chamber angle (ACA) and subsequent increase in intraocular pressure that leads to glaucomatous optic neuropathy.[2] The current reference standard for evaluating the ACA is by gonioscopy, a technique that requires a high level of expertise and the examination involves direct contact with the patient's eye. Angle closure is considered in an eye when there is no visibility of the posterior trabecular meshwork (usually pigmented) in at least two gonioscopic quadrants.[3] In addition to gonioscopy, in the past decade, anterior segment optical coherence tomography (AS-OCT) has been incorporated in routine ophthalmic practice to help assess the configuration of the ACA.[4,5] Especially in nonspecialist ophthalmology practice, gonioscopy may be less frequently performed and AS-OCT may not be available, leading to the need of other anterior segment evaluation methods.

Beyond these two commonly employed methods, there are several modalities that can assess the risk of angle closure based on useful clinical surrogates, such as the anterior chamber depth (ACD). ACD is regarded the most important risk

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Submission: 14-07-2021
Accepted: 26-09-2021
Published: 10-12-2021

How to cite this article: Porporato N, Bell KC, Perera SA, Aung T. Non-optical coherence tomography modalities for assessment of angle closure. Taiwan J Ophthalmol 2022;12:409-14.

factor for angle closure.[2,6,7] ACD can be subdivided into central ACD or limbal/peripheral ACD. Central ACD is defined as the distance between the corneal endothelium and the anterior capsule of the crystalline lens. It can be measured with several devices, such as interferometry and ultrasound biometry, AS-OCT, Scheimpflug photography, and the scanning peripheral ACD analyzer (SPAC). However, it can also be estimated with the oblique flashlight test.[8] Evaluating ACD has long been recognized as screening tool for primary angle-closure glaucoma in the Asian population and continues to be important, as studies show a relative risk of peripheral anterior synechiae (PAS) of up to 18 in patients with ACD between 2.00 and 2.19 mm and even higher in ACD smaller than 1.79 mm.[7] The limbal ACD is the closest to the ACA, and thus, contact between the peripheral iris and the corneal endothelium at this level is likely to represent angle closure in that quadrant. The modalities to assess the limbal ACD include the van Herick test and the SPAC device.

More recently, goniophotographic systems have been developed to document the anatomy of the ACA. For the first time, these systems produce images of the ACA similar to those seen with manual gonioscopy. The technology used is based on the combination of a lens, different lighting systems, and digital cameras, but, similar to conventional gonioscopy, all the available devices require a coupling gel and contact with the patient's eye. NGS-1 automated gonioscope (NIDEK Co., Gamagori, Japan) is the only device commercially available with a specialized software for ACA imaging. The RetCam (Natus Medical Incorporated, Pleasanton, CA) is a handheld retinal camera and can also be used to visualize the ACA although its software was developed exclusively for screening of retinopathy of prematurity. Several prototype devices for angle imaging, such as the GonioPEN and Axicon lens assisted gonioscopy, are currently being developed.

In this article, we aim to review different modalities of ACA assessment, beyond AS-OCT, as they could be of help for the physician in a variety of clinical settings. We will compare their relative advantages and disadvantages and how well they compare with the reference standard of manual gonioscopy in assessing for angle closure.

Methods to Assess the Anterior Chamber Depth

The oblique flashlight test

The oblique flashlight test is a simple method that has been used in many population-based studies to assess the risk of angle closure.[6,9-11] The test involves shining a penlight from the temporal side of the eye, perpendicular to the nose and parallel to the iris. A shadow is projected to the nasal side of the iris, with its width of the shadow varying according to the ACD, i.e., the shallower the ACD, the wider the shadow [Figure 1]. Different grading systems have been proposed to subjectively or objectively measure the shadow width. For the objective classification system proposed by He *et al*., the cut-off that holds the higher risk of angle-closure is Grade 1 that corresponds to a shadow that reaches the pupil margin and an iris-shadow ratio of 0.18.[8] The iris-shadow ratio is calculated as the shadow width over the limbus to limbus distance measured in the slit lamp. From a meta-analysis, the sensitivity of this technique was reported to be 0.51 (0.25–0.76) and the specificity, 0.92 (0.70–0.98) for the cut-off Grade 1, with a low level of certainty.[12]

The greatest advantage that oblique flashlight method holds is that it can be performed without any special equipment or slit lamp, making this method accessible even to people in rural regions. It can be also performed by nonspecialized physicians who may want to assess the risk for angle closure in the evaluation of subacute angle closure symptoms or before the prescription of certain medications that can trigger acute angle closure in predisposed eyes.

The van Herick technique (limbal anterior chamber depth assessment)

This technique was described by van Herick *et al*. in 1969[13] and requires the use of the slit lamp. It assesses the peripheral ACD by setting a vertical beam of light near the limbus, with the illumination system 60° apart from the biomicroscope [Figure 2]. The depth is calculated as a fraction (or percentage) of the corneal thickness over the central portion of the beam. There are two classification systems: based on the original classification by van Herick and its modification by Foster *et al*.[14] He changed the original 4-point grading system to 7 points to improve precision. A Grade 2 or less (equivalent to ≤25% cornea thickness) requires gonioscopy to confirm angle closure while a Grade 1 (or ≤15%) is at a high risk of angle closure. Its reported overall sensitivity was 0.83 (0.74–0.90) and specificity 0.88 (0.84–0.92) for the cut-off ≤25% corneal thickness.[12] However, the intraobserver repeatability of the test was only moderate (Kappa between 0.48 and 0.56).[15,16]

This technique is still widely used in clinical practice for screening purposes, especially to rule out angle closure. One of the biggest advantages of this method is that it is easy to assess during the slit-lamp evaluation, and its diagnostic performance was reported to be similar to more advanced imaging techniques, such as AS-OCT.[17] However, one of the main problems with this technique

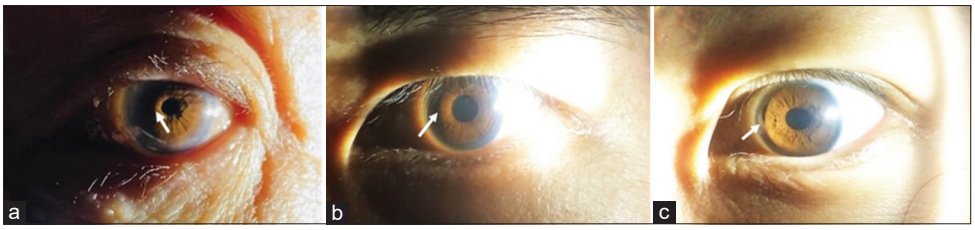

Figure 1: Classification of the flashlight test. Arrows (white) showing iris shadow reaching pupillary margin (a: Grade 1), in the middle between the pupillary margin and corneal limbus (b: Grade 2) and almost not shadow or closer to corneal limbus (c: Grade 3)

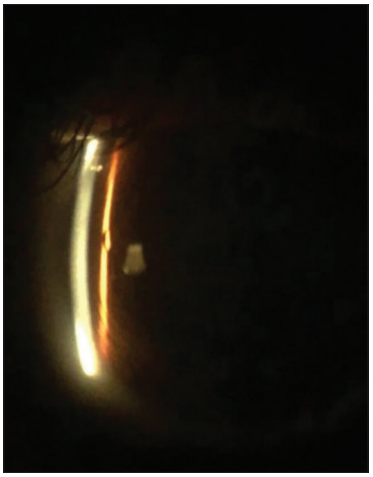

Figure 2: van Herick technique (limbal anterior chamber depth assessment)

is the subjectivity of the measurement, as it can be affected by the position of the light beam, leading to a low repeatability and reproducibility.

Scanning peripheral anterior chamber depth analyzer

The SPAC is a method that can objectively assess the peripheral ACD. SPAC automatically takes 21 slit-lamp images from the peripheral to central anterior chamber [Figure 3].[4,18,19] The device provides two different measurements. The first one evaluates the ACD itself from a numerical scale, where 12 represents the deepest ACD. The second measurement available is a categorical grading of the risk of angle closure: "S" for angle closure suspect, "P" for potential angle closure, and "N" for normal. The device has been shown to be reproducible and easy to operate.[4,18] The intraobserver and interobserver variations were reported to be small (mean coefficient of variance of 7.4% and 6.7%, respectively) but the agreement of the measurement tended to decrease from the center to the limbus.[20] The SPAC has been shown to correlate fairly with the modified van Herick system in grading peripheral ACD (*R* coefficient ~0.54).[21] A recent meta-analysis reported an overall sensitivity of 0.83 (0.70–0.91) and specificity 0.83 (0.70–0.91) for the cut-off ≤5 and/or S or P to detect gonioscopic angle closure, with a moderate level of certainty.[12]

This device can be conveniently attached to the slit lamp. In contrast with the van Herick technique, SPAC had a high reproducibility and repeatability, as it provides an objective measurement of the ACD that does not rely on the examiner's interpretation and is noncontact. However, its diagnostic performance was not shown to be superior to the van Herick technique.[12]

Scheimpflug photography

The OCULUS Pentacam (Oculus, Wetzlar, Germany) can provide more rapid and quantitative images compared to the conventional gonioscopy. It is a noncontact device and works by taking radially oriented photographic images from a rotating camera. This provides ACD measurement, among other common quantitative biometric parameters. This system delivers a utility potentially similar to AS-OCT.[12] When screening eyes with angle closure, an ACD cut-off point of 2.58 mm resulted in 100% sensitivity and 87.1% specificity.[22] The pooled sensitivity for ACD was reported as 0.92 (0.84–0.96) and the pooled specificity as 0.86 (0.76–0.93).[12]

Angle Photography Systems

Goniophotography systems

These systems are able to image the anatomy and configuration of the ACA and are useful for documentation of the gonioscopic findings. There are two commercially available devices, the RetCam [Natus Medical Incorporated, Pleasanton, CA, Figure 4] and NGS-1 automated gonioscope [NIDEK Co., Gamagori, Japan, Figure 5]. There are also two prototype systems, the GonioPEN [Figure 6] and axicon lens assisted gonioscopy adapted to the slit lamp. Goniophotography is used to document the angle structures using a slit lamp camera and a 2 mirror goniolens applied to the anaesthetized eye with a coupling gel. The amount of light can be adjusted from wide beam to slit beam depending on what view is needed. It requires someone who is well versed in gonioscopy as well as photography to take the best images. As these systems require contact with the patient's eye, some discomfort can be experienced.

The RetCam, a handheld retinal and angiographic camera, can be used to document the ACA when using its B1200 lens and 120° of field view. It had a reported overall sensitivity of 76.2% and specificity of 80.9%, with area

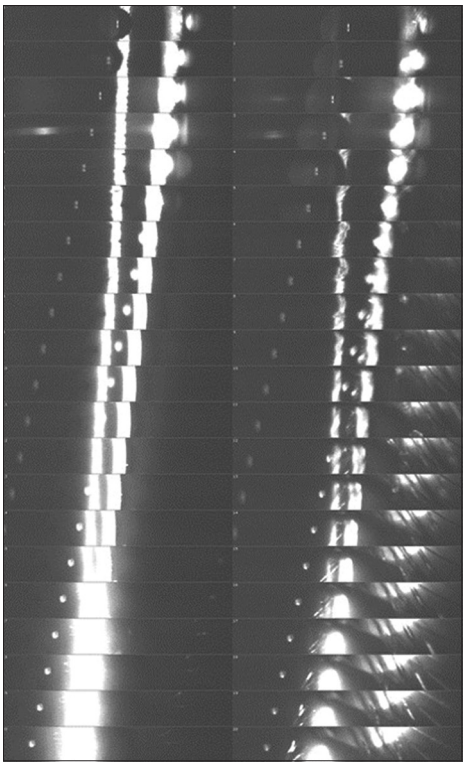

Figure 3: Scanning peripheral anterior chamber depth analyzer output

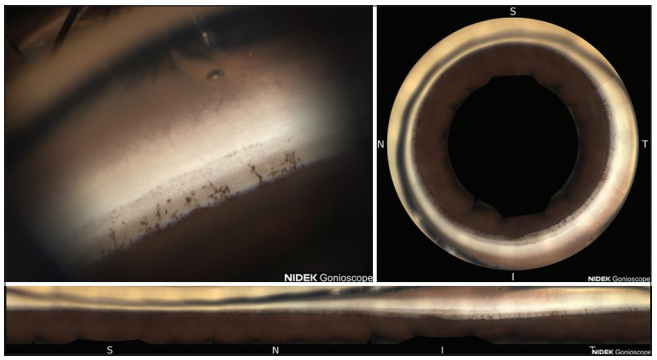

Figure 5: NGS-1 Gonioscope output

under the curve (AUC) of 0.79 to detect gonioscopic angle closure and its agreement with manual gonioscopy was reported to be good (first-order agreement coefficient between 0.72 and 0.76).[23-25] Baskaran *et al*.[26] compared gonioscopy and both manual and automated grading of RetCam images based on machine learning and the agreement for angle closure diagnosis was found to be good (κ = 0.88 and κ = 0.74, respectively). The AUC for detecting eyes with gonioscopic angle closure was comparable for manual and automated grading (AUC 0.97 vs. 0.95, $P = 0.31$) of RetCam images. In a different study, the use of RetCam with goniophotography for angle assessment was compared, using gonioscopy as the reference standard. It showed a very good diagnostic performance for angle closure diagnosis using both these modalities compared to gonioscopy, especially using the

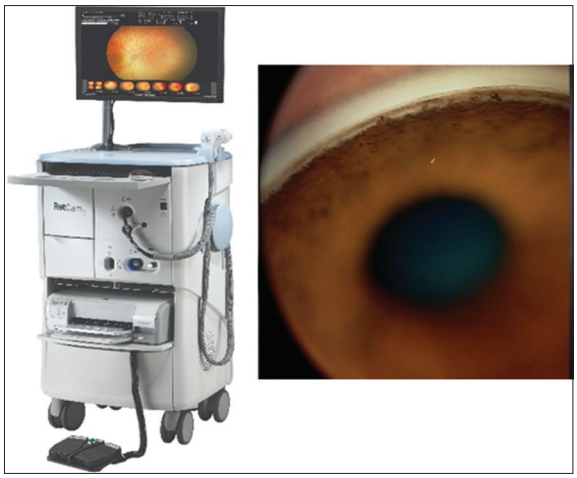

Figure 4: RetCam device and output

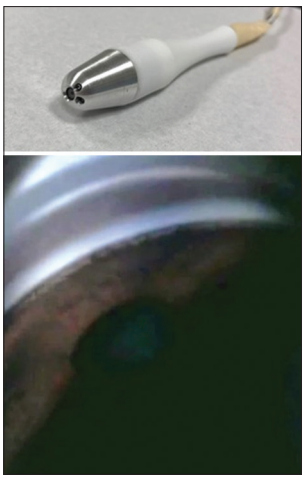

Figure 6: GonioPEN (α prototype)

two-quadrant definition of angle closure. Both techniques identified more angle closure compared to gonioscopy but the difference was not significant.[23]

The most recently commercialized device for angle photography is the NGS-1 automated gonioscope (Nidek Co., Ltd, Gamagori, Japan).[27] This device requires contact with the patient's eye as it captures 16 sections across the 360° of the ACA in <1 min. Four photographs are automatically taken per section, and the in-built software selects the one with the best quality. However, the user can reselect the image that they consider to be the best. Not all eyes are able to be imaged with this device, as it requires good fixation, corneal transparency, and reasonable patient cooperation.[28] Among glaucoma specialists, it had a poor to fair agreement with manual gonioscopy (κ = 0.22–0.58) and interobserver (κ = 0.17–0.38) and a fair to moderate intraobserver agreement (κ = 0.32–0.76).[29] It has been reported in a meeting abstract that it can document PAS, abnormal iris processes, anterior embryotoxon, blood vessels, minimally invasive glaucoma surgery implants,

filtering surgeries, and glaucoma drainage devices.[30] The NGS-1 stands out for its short capture time and for its shorter learning curve than manual gonioscopy. However, the main problem with this technology is the resolution of the trabecular meshwork due to focus. Furthermore, the interpretation of the images still requires physician experience.

The GonioPEN combines a high-resolution miniaturized integrated charge-coupled diode camera and light emitting diode light source-based probe system. The probe can be conveniently attached to a slit lamp and has to be placed near the limbal region of the cornea to image the opposite iridocorneal angle.[31]

The axicon-assisted gonioscopy is a flexible handheld probe that uses a gonioscopy imaging approach by integrating Bessel beam microscopy concept and can image the ACA with spatial resolution down to 3 μm. It has a better structural clarity image of the trabecular meshwork as compared with the other Goniophotograph systems. It has an imaging sensor located at the central axis of the probe and has a variable resolution at different depths which is optimized for recording the ACA of the eye.[32]

Conclusions and Future Directions

Although the clinical evaluation of the ACA by the gonioscopy remains the gold standard for angle-closure assessment, different techniques can also be implemented to estimate its risk with easy-to-asses surrogates, such as the peripheral ACD. They each have their role in a particular context. For screening purposes in a primary care ophthalmic facility, the van Herick or limbal ACD assessment seems a potentially suitable technique as it is simple with high sensitivity (83%) and specificity (88%). Goniophotography systems compromise promising tools for documentation of gonioscopic findings but its interpretation relies on observer expertise. Some work has been done to automatize the interpretation of these images.[26] However, it has not been widely incorporated in the clinical practice yet and the evaluation of its agreement with manual gonioscopy and its diagnostic performance for angle closure remains to be assessed. Looking forward, the combination of these techniques with new technology, such as machine learning, could potentially increase their accuracy and help especially the nonspecialist when screening for risk of angle closure in Asian patients. This opens the field for further exploration.

Financial support and sponsorship
Nil.

Conflicts of interest
The authors declare that there are no conflicts of interest of this paper.

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