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Angle Closure Glaucoma: Pathogenesis and Evaluation. A Review

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Abstract

Primary open angle glaucoma (PACG) is a major cause of blindness especially in Asia. The pathogenesis of this condition has been widely investigated. Traditionally gonioscopy is the method of choice for the esamination of patients considered to be at risk for angle closure, but it is a rather invasive procedure and it is reported to be primarily used by glaucoma specialists. Recently newer ultrasound and optical methods for the evaluation of the anterior chamber angle have been introduced in the clinical practice, with distinct advantages and disadvantages both compared to each other and to gonioscopy. This review will address the pathogenesis of PACG, the use of gonioscopy and will evaluate the newer methods of angle examination.

Terminology

It has been suggested that the development of meaningful evidence on the diagnosis and management of primary angle closure glaucoma has been hindered by inconsistent approaches in the classification of the disease. Three conceptual stages of angle closure have been identified and described, originating a new well accepted classification of this entity.

PAC (Primary angle closure) is an anatomical disorder of the anterior segment of the eye characterised by permanent closure of part of thefiltration angle as a result of previous iris apposition to the trabecular meshwork. The subsequent rise in intraocular pressure can cause optic nerve damage and is defined as primary angle closure glaucoma (PACG). Primary angle closure suspects (PACS) or anatomically narrow angles (ANA) do not have any anatomical or physiological damage from irido-trabecular contact (ITC), but have an anatomical predisposition to closure [1]. Differential diagnosis with open angle glaucoma (POAG) is essential because initial therapy is different and because the rate of complications with filtering surgery are higher in PACG compared to POAG patients.

Epidemiology

It has been estimated that 67 million people worldwide are affected with a primary glaucoma and that one-third have PACG [2]. In European and African populations primary open-angle glaucoma (POAG) occurs approximately five times more frequently than PACG; in Chinese [3,4] Mongolians [5] and Indians [6] however, the rates of PACG may equal or be greater than POAG. In Eskimos/ Inuit the prevalence of PACG is felt to be higher than any other ethnic group [7].

Comprehensive studies in European populations documented more than 25 years ago that anatomical risk factors for angle closure include smaller anterior chamber width, area, and volume, thicker iris with greater curvature, and increased lens vault. There is increasing recognition that physiological factors, such as increase in iris volume with dilation and choroidal expansion, may also have a significant role in angle closure.

In small eyes predisposed to angle closure, choroidal expansion leading to increased vitreous cavity pressure, may be a contributing cause [8].

Pathogenesis

There are two basic mechanisms responsible for closure of the angle: pupillary block and angle crowding.

Pupillary block is the most common mechanism responsible for angle closure [9], but the anatomical configuration which causes a plateau iris may be a more common mechanism than was previously thought.

Pupillary block mechanism

In pupillary block, the resistance to aqueous flow from the posterior to anterior chamber is at the level of the pupil, creating a pressure gradient that causes forward bowing of the peripheral iris and closure of the angle [10,11].

Aqueous humor flow from the posterior chamber into the anterior chamber is regulated by a differential pressure between the anterior and the posterior chamber. This pressure differential may increase greatly when the dimensions of the iris-lens channels are changed. As this pressure increment increases, the iris becomes more convex and can close angle.

Extreme anterior iris-bulging, iris bombé would be expected with pressure differentials of 10-15 mm Hg [12]. The variables that influence the flow through the "pinch region" (iris-lens channels) and influence the pressure differential and related iris contour have been studied extensively [12-16].

Changes in pupillary size, increased channel length and decreased height, movement of the iris insertion posteriorly or of the lens anteriorly, were associated with an expected increase in the pressure differential. Other variables exist and interact to determine the iris contour, including eye size, especially the dimensions of the anterior segment, lens size and position, iris stroma and iris musculature characteristics, ciliary body anatomy, and physiologic parameters including aqueous humor flow rate, facility of outflow, vitreous-aqueous fluid flow, and the effects of accommodation and blinking [9].

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Angle crowding

This mechanism for angle closure may exist alone, but more often co-exists with pupillary-block. Angle crowding can be thought of as the sandwiching of the peripheral iris occluding the trabecular meshwork, compared to the pupillary-block related anterior iris shift secondary to the pressure differential between the anterior and posterior chamber. The clinical primary condition possessing this mechanism is the plateau iris configuration [17].

Plateau iris

Plateau iris configuration denotes an angle appearance in which the iris root sharply angulates forward and then centrally. The iris surface appears flat (hence the term "plateau"), and the central anterior chamber is of relatively normal depth. Primary plateau iris is associated with a large or anteriorly positioned ciliary body that physically supports the iris root against the trabecular meshwork (Figure 1, 2) [18,19].

The term plateau iris syndrome refers to the development of angle closure despite the presence of a patent iridectomy.

Depending on the amount of trabecular obstruction caused by iris root, acute or chronic angle closure can occur. The latter is more common and clinically significant because these patients may develop peripheral anterior synechiae (PAS) years after a successful iridotomy in apparently a well-opened angle.

Peripheral anterior synechiae

Prolonged or repeated apposition of the iris to the trabecular meshwork leads to gradual PAS formation.

PAS were most frequently found in the superior part of the angle, which may be due to corneal flattening due to upper eyelid pressure [20].

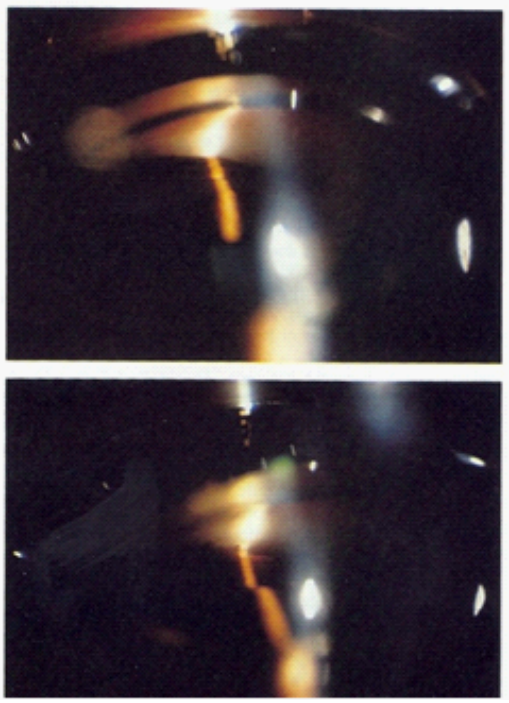

Figure 1: Plateau iris: without indentation (A), with indentation (B).

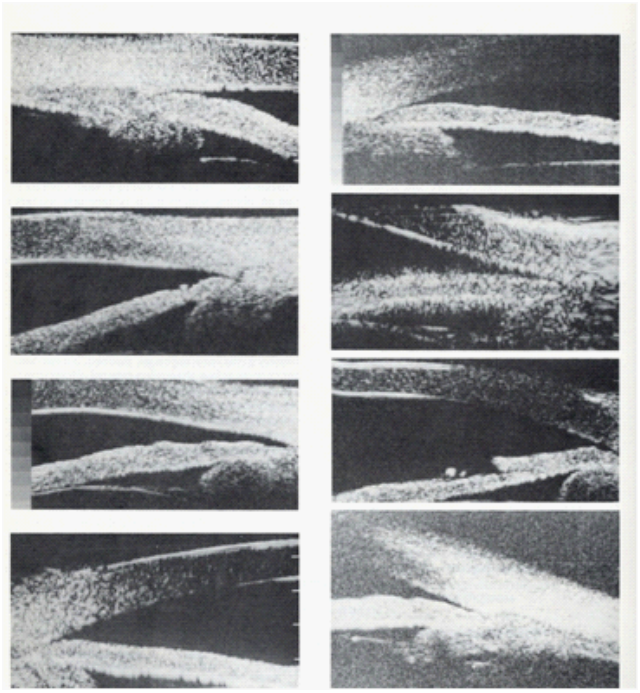

Figure 2: Ultrasound biomicroscopic images of typical angle cross sections in eyes with the palateau iris syndrome. These images show variations in degree of angle closure and in configuration of the iris and ciliary processes. They all have in common an anterior positioning of the ciliary processes, which produces an absent ciliary sulcusand consequent narrowing of the angle.

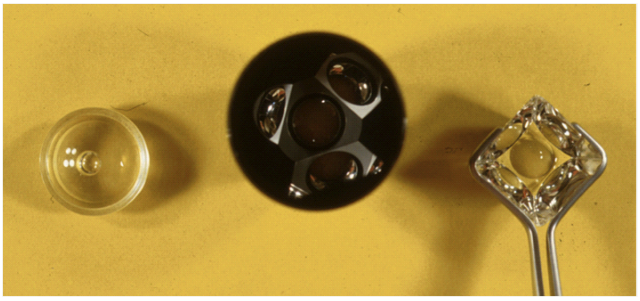

Figure 3: Gonioscopy Leneses: from the left to the right Koeppe, Goldman 3 morrors and Zeiss 4 mirrors lenses.

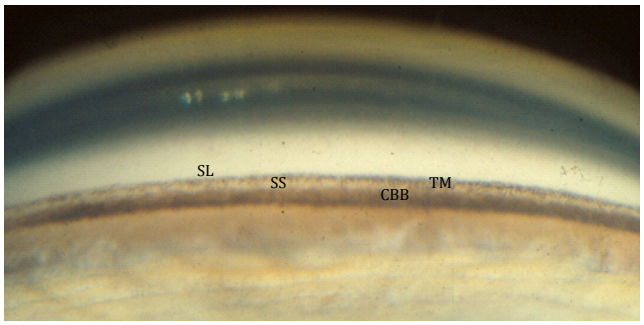

Figure 4: Gonioscopic view of the ACA (A) Gonioscopic appearance of the normal anterior chamber angle. Schwalbe's line (SL), trabecular meshwork (TM), scleral spur (SS), and ciliary body band (CBB) all are visible in this open angle.

Eventually, a critical fraction of the circumference of the trabecular meshwork becomes permanently closed with synechiae. At this point, the remaining fraction of the angle that is still open provides insufficient facility of outflow to keep pace with aqueous production, and the IOP rises. Closure of one half to two thirds of the angle with PAS results in permanent elevation of IOP.

The synechiae are initially narrow reaching to the mid trabecular meshwork and then gradually expand in width.

The second pathway refers to a circumferential angle closure and begins in the deepest portion of the angle. Although the closure occurs more evenly than with pupillary block, there is often slight asymmetry and the superior part of the angle is usually interested before the inferior part. The appearance over time is that of a progressively more anterior iris insertion [21].

Gonioscopy

Gonioscopy is the current reference standard for evaluation of the anterior chamber angle (ACA). Gonioscopy is performed for several reasons: 1) to determine the mechanism of glaucoma (i.e. open or closed angle, pigment dispersion, plateau iris, etc.); 2) to identify persons at risk of developing angle closure glaucoma; and 3) to monitor changes in the ACA over time as part of clinical care or research. Viewing the ACA of a normal eye directly is impossible, because the light from the junction of the iris and cornea strikes the tear-air interface at a shallow angle, and it is totally reflected back (total internal reflection). Contact lenses are used to overcome this problem. Depending on lens used, the ACA can be visualized by direct or indirect methods.

Direct gonioscopy provides a straight-on view of the angle (rather than the mirror image given by the indirect lenses) and permits the examiner to vary more readily the angle of visualization. The view is more panoramic than with indirect lenses, but it is poorer of detail and localization of angular structures is somewhat more difficult.

Indirect lenses have several advantages that have made them the preferred lenses for most ophthalmologists. No special equipment is required when performing indirect gonioscopy. The slit lamp is used as a source of variable magnification and illumination and the slit beam can be used to identify the "corneal wedge" (Figure 5), which indicate the Schwalbe's line and is useful to locate the anterior border of the trabecular meshwork. Indentation gonioscopy can be also performed to distinguish appositional from synechial angle closure. The disadvantage is to give a mirror-image view of the angle, which can be confusing. It is also easy to open or close the angle inadvertently by applying excessive pressure to the indirect lenses.

Direct gonioscopy

Direct gonioscopy is performed with a convex lens, which permits light from the angle to exit the eye closer to the perpendicular at the interface between the air and the lens. The Koeppe lens, wich is a 50 D lens (inner radius of curvature 7,5 mm and outer radius 12,5 mm), is placed on the cornea while the patient is in the reclined position [22]. A magnification of 1.5 x is obtained but the examiner requires a hand-held unit (Stereoscopic viewer, Haag-Streit, Bern, Switzerland) for further magnification and illumination (up to 16 X). Koeppe lenses are available in sizes from 16 to 22,5 mm in diameter, although most adults can be examined using the 16 or 18 mm lens. Larger lenses can be used if limbus is irregular or in the presence of a filtering bleb. Other direct lenses are the Swan-Jacob and the Hoskins-Barkan ones, which are designed for performing surgical procedures such as goniotomy and goniosynechialysis. Direct gonioscopy is performed rarely since the introduction of indirect lenses, which are more convenient and more readily available to the average clinician.

Indirect gonioscopy

In indirect gonioscopy, mirrors are used to overcome the total corneal internal reflection. They redirect the light from the angle so that it exits the eye perpendicularly to the lens-air interface.

The examination is performed at the slit lamp and takes advantage of the latter's flexible illumination and magnification system. The base curvature is the major feature that distinguishes the various indirect gonioscopy lenses [23]. Smaller lenses (corneal type lenses: Posner, Sussman and Zeiss lenses),

Lens	General features	Type	Advantage	Disadvantage
Koeppe	Available in small, medium and large size.	Direct	Convenient for examination under anesthesia (EUA), no angle distortion, allows the view of the fundus, easiest for angle photography, excellent panoramic view.	Patient must be in supine position, laborious examination patient dislikes, examiner must change position, operating microscope required.
Barkan	Available for adults and for children	Direct	Surgical goniolens with blunted side allows access for goniotomy, variable sizes.	Same as Koeppe.

Table 1: Direct Lenses.

Lens	Type	General features	Advantage	Disadvantage
Zeiss 4-Mirror	Indirect	DIMENSIONS 9 mm diameter inner radius 7.85 mm MIRRORS 4 mirrors 12 mm high Angle 64 degrees	Rapid evaluation without goniogel, further same-day diagnostic tests not compromised, patient friendly, slit lamp friendly with minimal movement to see 360°,option for compression to perform indentation gonioscopy.	Must first master Goldmann gonioprism, more hand-eye co-ordination necessary than for Goldmann gonioprism, easy to apply excessive force causing corneal folds with poor view of angle.
Posner	Indirect	DIMENSION 9 mm diameter inner radius 8.13 MIRRORS Angle 64 degrees	Same as Zeiss	Same as Zeiss
Sussman	Indirect	DIMENSION Same as Posner, withouth handle MIRRORS Angle 64 degrees	Same as Zeiss	Same as Zeiss

Table 2: Indirect corneal type lenses.

have four mirrors and a 9-mm diameter corneal surface (radius of curvature 7.72 mm) so there is no need to apply a coupling agent before placing it on the cornea. This not only simplifies the process of performing gonioscopy, it also leaves the anterior segment clear for later viewing of the posterior pole. This type of lens can more easily compress the cornea, leading to image distortion and misinterpretation of angle structures, angle widening or narrowing depending on how the compression is placed [24]. The opportunity of compressing the cornea, however, allows for greater dynamic assessment of angle structures. For these reasons, corneal type lenses require greater expertise and training than using the coupled, steeper base curve lenses.

Those with base curves extending to the sclera (scleral type lenses: Goldmann, Allen/O-Brien, Allen-Thorpe, Ritch and the Magna View lens) are the most commonly used. They have larger base diameters (12-mm diameter and a radius of curvature of 7.38 mm) and require a coupling agent to fill the gap between the lens and the cornea. A major advantage of this style lens is the fact that it can be held squarely on the eye without distorting the cornea, resulting in a clear view of angle structures, although the angle can be artefactually narrowed or widened even using this kind of lenses [25,26]. Manipulation of the view (with some degree of indentation) can be performed with Goldmann- style lenses as well, and the angle can be opened using this technique in most cases [4,5,27-29]. By having the patient look in the direction of the mirror and pressing down over the mirror, one can indent the central cornea and open the angle.

The most commonly used lens is the Goldmann-type 3-mirror (Universal) lens that has one mirror dedicated to viewing the angle (thumb-nail-shaped mirror), but other models are commonly used and their characteristics are reported in table 3.

The Goldmann lenses use a mirror to reflect the light emanating from the angle, whereas Allen/O-Brien and Allen-Thorpe lenses rely on prism.

The Ritch trabeculoplasty laser lens is similar to the Goldmann lens except that all four of its mirrors are dedicated at the angle. The Magna View lens (Ocular instruments) is a Goldman-like one mirror lens that has been recently introduced. It has a broader viewing area than the Goldmann single-mirror lens and a convex anterior face that provides slight magnification. This lens was designed for the delivery of laser energy to the angle (Figure 3).

Viewing and Interpreting the Angle

The anatomical structure that may be seen when considering a wide open angle from anterior to posterior begin with Shwalbe's line, the the trabecular meshwork and scleral spur, and finally the scleral spur and ciliary body [22] (Figure 4).

Not only manipulations of the lens, but illumination conditions can dramatically change the aspect and the viewing of the angle. When a patient looks toward the direction of the examining lens or when the lens is slightly tilted, an angle considered closed in primary gaze, appears open [4,5,25,30,31].

Similarly angles closed when examined in the darkest possible condition may appear open when the illumination is increased. These angles are prone to appositional closure throughout the day. In addition, the width of the angle may vary according to the position (size/state) of the pupil [32]. To overcome the possible sources of variability, the current recommened approach is to examine the angle in primary gaze, with a small light beam: if no angle structures are visible the individual is considered at risk of angle-closure. It is highly recommended to identify Schwalbe's line because this is the foremost reference point in the angle examination (Figure 5).

Manipulation of the lens should be limited to closed angles only to determine if that specific angle is closed because of apposition or if there are PAS. Applying gentle pressure on the lens is warranted to distinguish apposition from synechial angle closure.

Indentation Gonioscopy

This technique helps the examiner distinguish between synechial and appositional angle closure. Here, the lens isdeliberately pushed against the central cornea, displacing aqueous to the peripheral anterior chamber andpushing the iris and lens posteriorly [24].

Sliding the lens slightly toward the angle being viewed often helps reduce corneal folds and improves the view. Pushing the iris backward not only opens the angle but allows for the viewing of the peripheral anterior synechiae (PAS) (Figure 6).

During indentational maneuvers, iris processes must not be confused with PAS. Although PAS are frequently discussed in research and are an important clue to the likelihood of angle closure, no standard approach to defining PAS exists in the literature. Foster has attempted to distinguish between PAS and iris processes and noted that PAS typically are broader at the base than at the apex, more elevated than iris processes, and have a more saw-toothed pattern [33]. How wide they have to be is unclear, and distinguishing PAS from iris processes may sometimes be problematic. Lichter reported that fewer than 10%

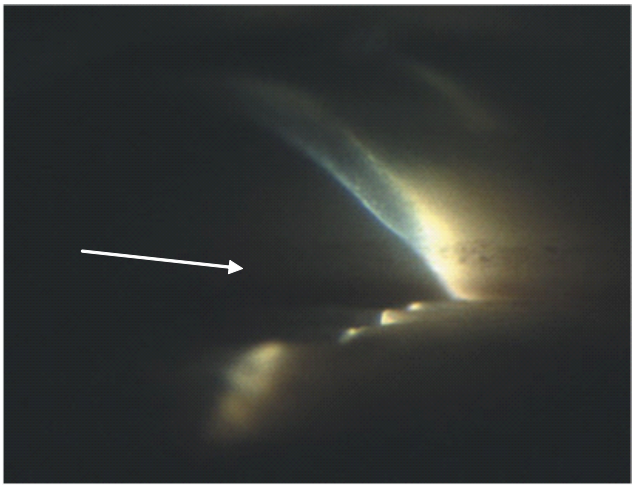

Figure 5: The Schwalbe's line (arrow) as can be seen using a thin slit beam angled 30 to 60 degrees from the viewer's gaze.

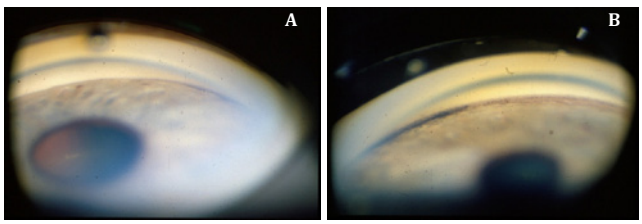

Figura 6: Gonioscopically apparence A) before indentation B) during indentation.

of a relatively young population had iris processes. There was no association between iris processes and IOP in this population.

One of the earliest reports on PAS referred to "pigment bands", which were clearly seen after iridectomy. They were felt to contribute to the failure of some persons to have normalized IOP after iridectomy [34]. Foster and colleagues reported that PAS were more prevalent in persons with narrow angles with a monotonic relationship between angle width and the presence of PAS [35]. Nevertheless even some with mean angle width over 30 degrees had PAS. Similar findings were reported by He and colleagues in a population based study in southern China [28]. In subjects with IOP >21 and PAS, enrolled in a multicenter Asian study, the mean number of clock hours of PAS was 4.8. There was weak correlation between the number of clock hours of PAS and the gonioscopic angle width (adjusted $p = 0.024$), [36] but the number of clock hours of PAS was correlated with IOP (adjusted $p < 0.001$). The development of PAS is pathologic. Two studies have documented that higher IOP is associated with the presence and amount of PAS [31,36]. Appositional closure may damage the trabecular meshwork prior to the formation of PAS [37]. Why some persons with narrow angles develop PAS and others do not is still unknown. A better understanding of this issue will help clinicians determine who should be monitored or undergo a laser iridotom.

Grading Schemes

A highly reproducible approach and grading scheme are essential requisites for appropriate classification of persons as having open, at-risk, or closed angles. The ACA anatomy is complex. Because natural history data are lacking, it is unclear which angle findings predict clinical outcomes, and which persons are at high risk of suffering harm due to narrow or closed angles. Several grading schemes have been proposed for documenting angle findings seen on gonioscopy, most notably those by Shaffer, Scheie, and Spaeth [23]. A recent consensus document published by the Association for International Glaucoma Societies proposed that the ACA should be viewed in a dark room using a 1-mm beam with adequate illumination to visualize angle structures clearly with the patient looking straight ahead.This approach allows one to see the corneal wedge, it minimizes the angle-opening effect of illumination, and it avoids artifactitiously widening the angle by manipulating the lens.

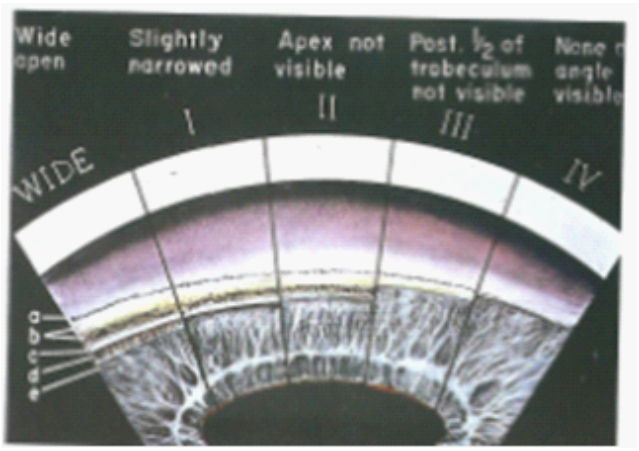

Figure 7: Sheie grading system. (Reprinted from Scheie , Arch Ophthalmol 1957; 58: b510-512 with permission of Archives of Ophthalmology.)

Scheie System

The ability to see ACA structures is the key element in this grading system. Roman numeral is used to describe the degree of angle closure. Larger numbers signify a narrower angle. The term "wide" or grade zero is used to describe an angle in wich all structures are visible. Scheie believed that persons with grade III and grade IV angles were at greatest risk of angle-closure glaucoma. In addition to grading the structures seen, Scheie also described angle pigmentation on a scale fro 0 (no pigmentation) to 4 (heavy pigmentation) and was one of the first to divide the trabecular meshwork into pigmented and non-pigmented regions [32] (Figure 7). There is no available study on the reproducibility of this grading scheme either within an observer or between observers.

Shaffer System

A more commonly used grading system is that of Shaffer [38,39].

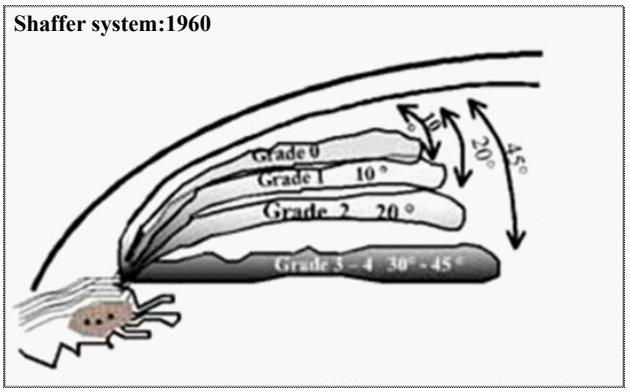

Figure 8: Shaffer grading system. Modified from Duane's Clinichal Ophthalmology Chapter 24 Figure: 10 http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v3/v3c044.html.

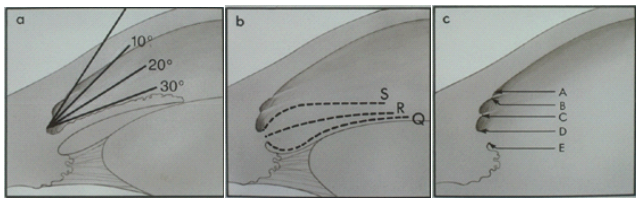

Figure 9: Spaeth grading system : a)angle of iris insertion, b)iris configuration, c) level of iris insertion. Modified from Tarrant (http://arapaho.nsuok.edu/~fulk/kanski.html).

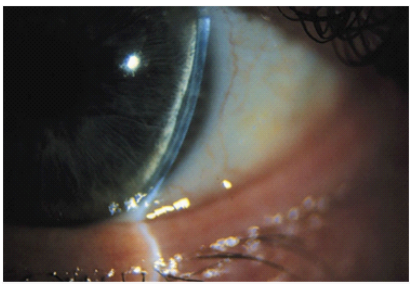

Figure 10: Van Herick grading system: grade 2 .

This system describes the degree to which the angle is open rather than the degree to which is closed, using arabic numerals. Whereas Sheie's grade IV denotes a closed angle, on the Shaffer scale grade 4 refers to a wide-open angle.

This scheme determines the angle width based on two lines: one drawn as a tangent to the peripheral third of the iris and the other drawn from the angle depth to the Schwalbe's line [40].Angles between 35° and 45° are grade 4, those 20° -35°are grade 3, those 10° - 20° are grade 2, and those ≤10° are grade 1, with a closed angle (zero degrees) is grade 0. Shaffer also reported the structures that should be seen for each of these grades but this is confusing, as there are angles that may not fulfill both criteria. Current practice appears to be to use angle width when describing the angle using the Shaffer system and to use structures when describing the ACA using the Scheie system. No intraobserver reproducibility studies have been published. Those reporting inter-observer reproducibility have found weighted kappa values in the range of 0.6-0.7 using a Goldmann lens [4,5,11,31]. It is possible that the studies overestimated the reliability of the method due to the high number of normal subjects in the sample (Figure 8).

Spaeth System

Spaeth considered that available grading systems provided limited information and proposed a system that grades the three major features of the angle's anatomy: 1) the angle of iris insertion (described by estimating a tangent to the endothelial surface of the cornea, but the exact location along the curve or the cornea is not stated) and a tangent to the anterior surface of the iris, measured at the point of Schwalbe's line2) the configuration of the iris; and 3) the level of iris insertion (Figure 9 and Table 4).

Spaeth also graded posterior pigmented meshwork in the 12o'clock angle and the type and the number of iris processes.

The Spaeth system, compared to the others, is much more precise but also more complex because of the numbers of the structures that have to be evaluated simultaneously.

The Spaeth system is the only system that has been studied for its repeatability and comparability to UBM in 22 non consecutive patients. Five of the 22 subjects were excluded because the two observers did not agree on the gonioscopy findings. The correlation between UBM angle grade and Spaeth grade in the remaining 17 subjects was extremely high [23,41]. In this study Spaeth reported kappa values of 0, 8 or greater between observers analyzing a single UBM image on each eye [41].

Van Herick System

Van Herick (VH) used the slit lamp to estimate the width of the ACA [42]. A narrow slit beam is placed perpendicular to the most peripheral part of the cornea. The oculars are adjusted to give a view at an angle of about 60° from the light beam. The depth of the anterior chamber is graded by comparison to the thickness of the cornea: if the AC is deeper than the cornea is a wide-open grade 4; if the thickness of AC is a half of the cornea is a grade 3, if it is a quarter is grade 2 if it is less than a quarter of the corneal thickness the angle is dangerously narrow, graded 1 or 0. In a modified Van Herick grading system introduced by Foster in 2000 [27] the anterior chamber depth is expressed as a

Lens	Type	General features	Advantage	Disadvantage
Goldman 3-Mirror	Indirect	DIMENSION 12 mm diameter 3 mm flange width MIRRORS 3 mirrors 10-12 mm high, 9 mm wide effective field: 80 degrees Angle 59 degrees (gonioscopy mirror)	Excellent gonioprism for neophyte to learn anatomy, viscous bridge creates suction effect stabilizing eye for examination and laser therapy.	Goniogel required for best view which obscures patient's vision and may compromise further same-day diagnostic tests, corneal abrasion in compromised cornea, part of angle hidden in narrow-angled eyes, time consuming when necessary to evaluate both eyes, potential for artificial narrowing/widening of the angle.
Goldman 1 Mirror	Indirect	DIMENSION 12 mm diameter 1.5 mm flange width MIRROR 1 mirror 12 mm high, 9 mm wide Angle 62 degrees	Same as Goldman 3 mirrors	Same as Goldman 3 mirrors
Allen -Thorpe	Indirect	PRISMS 4-62 degrees mirrors	Same as Goldman 3 mirrors	Same as Goldman 3 mirrors
Ritch	Indirect	DIMENSION 12.5 mm diameter MIRRORS 2-64 degrees mirrors (superior angle viewing) 2- 59 degrees mirrors (inferior angle viewing) effective field: 90 degrees 17D plano-convex button over two mirrors (1.4 X magnification)	Same as Goldman 3 mirrors	Same as Goldman 3 mirrors
Magna View	Indirect	DIMENSION 15-18 mm MIRROR One 62 degree mirror 1.3 magnification	It has a broader viewing area than the Goldmann lens and a convex anterior face that provides slight magnification. This lens was designed for the delivery of laser energy to the angle.	Same as Goldman 3 mirrors

Table 3: Indirect scleral type lenses.

percentage of the corneal thickness at the temporal limbus with the slit beam direct perpendicular to the ocular surface (the illumination column is offset from the microscope axis by 60°). The grades are divided in ≥ 100%, 75%, 50%, 25%, 5% and 0% of corneal thickness (Figure 10).

This system can be rapidly performed on almost any patient and can be helpful in the evaluation of confusing angles because it gives a separate indication of depth of the angle. However, the test does not provide any information about the ACA except the depth. The VH grading system has been found to to have different efficacy for diagnosing angle closure in various studies [43] (Table 5, 6).

Thomas and colleagues in a study of 96 consecutive patients (with occludable angles) found that the VH grading system (grade ≤ 2) had 89.3% specificity and 61.9% sensitivity [44].

Congdon and colleagues in a study of 562 eyes found that the VH grade ≤ 2 had a sensitivity of 56% and a specificity of 95% for diagnosing PACG [45]. In this study the VH evaluation was performed by ophthalmologists. In a Japanese study by Kashiwagi and colleagues [47], 646 eyes grade 1 o 2 according to the Van Herick classification, underwent a gonioscopic examination and were classified according to the Shaffer grading system; 65.9% resulted to have narrow angles. In particular among those with VH grade 1, 86.3% had narrow angles, and with VH grade 2 it was 64.2%.

Foster and colleagues, in a population-based study from Mongolia, used a modified VH system: they found that the 15% grade (equivalent to traditional grade 1) had a sensitivity of 84% and a specificity of 86% for occludible angles. The interobserver agreement for this augmented grading scheme was good (weighted kappa 0.76) [27].

Nolan and colleagues, using a similar grading system, found 77% sensitivity and 91% specificity for VH grade 1 or less [49].

Baskaran and colleagues, with the modified VH grading system found 84.9% of sensitivity and 89.6% of specificity using VH grade 25% and below (equivalent to traditional grade 2). Using VH grade 15% and below (equivalent to traditional grade 1) sensitivity was 60.4% and specificity was 100% [43].

In a recent study of 148 consecutive patients, Park and colleagues founded good agreement in detecting angle closure between VH method and gonioscopy (K: 0.80, temporal; K: 0.82 nasal) [46]. Sensitivity was 92% nasal and 96% temporal, while specificity was 100% nasal and 90% temporal.

Sensitivity and specificity of the Van Herick test is variable and the difference is probably due to the different settings of the examinations (clinical vs population based studies), by the operator (ophthalmologists vs technicians). It is currently impossible to evaluate if the original VH test or the modified one perform better because some of the difference in the results can be due to the use of different diagnostic criteri.

Quantitative Gonioscopy

To improve the repeatability and the objectivity of gonioscopy, severalmethods of quantitative gonioscopy have been proposed.

In 1940 Sugar suggested the use of a graticule attached to the ocular of a magnifying lens to help improve the reproducibility of measurements of the angle width, but did not present data on the use of this technique [50].

In 1980 Cockburn reported a linear angle grading scheme in order to increase the reproducibility of gonioscopy findings [51]. His approach was to use the combined width of the trabecular meshwork and the scleral spur (using the corneal wedge to mark the start of trabecular meshwork) as a unit and to grade the angle width using these units. This approach was testedin 50 patients: the mean angle was 1.2 units and had reasonable intra-observer repeatability ($R^2 = 0.56$).

More recently, Congdon and colleagues attempted to improve

Iris insertion	Angular approach	Peripheral iris		Pigmentation of trabecular meshwork
A Anterior to Schwalbe's line	0 to 50 deg	r regular	f flat	0 no pigment
B Between Schwalbe's line and scleral spur		s steep	b bowed anteriorly	1+ minimal
C Scleral spur visible			p plateau iris	2+ mild
D Deep with ciliary body visible		q queer	c concave	3+ moderate
E Extremely deep with > 1 mm of ciliary body visible				4+ intense

Table 4: Spaeth gonioscopic grading system.

AUTORS	COUNTRY	SUBJECTS	CUT OFF	SENSITIVITY	SPECIFICITY	GOLD STANDARD	AGREEMENT	STUDY
Thomas et Al. 1996 [44]	India	96	VH 1	62%	89%	Gonioscopy		Clinical setting
Congdon et Al. 1996 [45]	Taiwan	562	VH 2	94%	58%	Diagnosis of PACG		Population-based
Park et Al. 2010 [46]		148	VH 1	92% nas 96% temp	100% nas 90% temp	60° of invisible TM each quadrant	K: 0.80 nasal K: 0.82 temporal	Clinical setting
Kashiwagi et Al. 2005 [47]	Japan	383	VH1 VH2	29.3% 70.7%	47.1% 9.7%	Shaffer grade 2	86.3% 64.2%	Clinical setting

Table 5: Sensitivity and specificity of the VH grading system

AUTORS	COUNTRY	SUBJECTS	CUT OFF	SENSITIVITY	SPECIFICITY	GOLD STANDARD	AGREEMENT
Cockburn 1982 [48]	Australia	1113	≤ 20%	89%	99%	Gonioscopy	
Baskaran et Al. 2007 [43]	Singapore	120	25% 15%	84.9% 60.4%	89.6% 100%	Shaffer grade <1 in at least 180%	AUC: 0.87 (Spearman)
Nolan et Al 2006 [49]	Singapore	1090	≤25% ≤15%	95.7% 83%	66.9% 88.1%	TM visible in less than 90°	AUC: 0.90

Table 6: sensitivity and specificity of the modified VH grading system

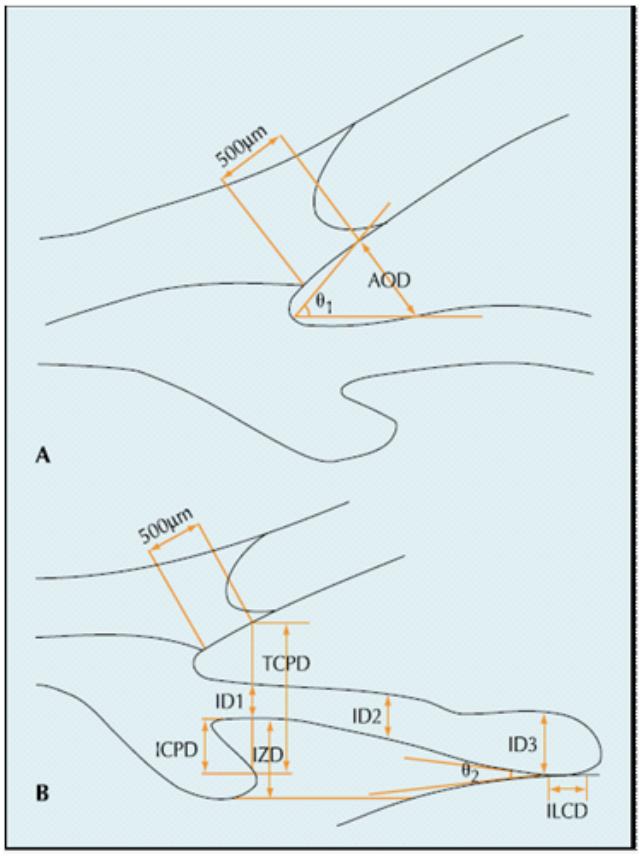

Figure 11: In the figure, the various measurements obtained with UBM are shown. Reprinted from Ishikawa and coll, 2000 [67] with permission of Current Opinion in Ophthalmology.

on this quantitative approach, and added a graticule to the slit-lamp ocular to allow standardized measurement of the length of the angle recess [52]. This biometric gonioscopy technique was tested on 21 subjects that were also imaged with the Sheimpflug camera and underwent gonioscopy with Spaeth grading by separate observer. Although biometric gonioscopy appears relatively reproducible, the units reported give no detail about the structures seen, and therefore the technique offers only limited insight into the angle configuration.

Neither of the two linear estimates of angle opening have been widely adopted [23].

Gonioscopy Findings

The ACA appears to be wider inferiorly and narrower superiorly [53-55]. This finding largely supports a non-quantitative assessment by Otto Barkan published in 1935. With age, the ACA tends to narrow [56-60]. The most likely explanation for a higher prevalence of PACG among older persons is the increase in lens thickness [61-63]. This leads to crowding of the anterior segment. In addition, it is postulated that the zonule becomes more lax with age, allowing anterior movement of the lens/iris diaphragm. Although it is clear that PACG prevalence increases with age, few studies have assessed the distribution of angle findings across a wide age range, and none to date have assessed a population prospectively to see how the angle configuration changes.

PACG is more common among women, but only one population-based study has concluded that women had narrower angles than men when using gonioscopy [35].

Spaeth assessed the impact of sex and age on angle configuration. He enrolled 759 white subjects 5 to 79 years of age. Spaeth found that the angle width decreased with increasing age, and that pigment in the angle increased with age, but there were no differences in angle configuration comparing men and women [41]. Congdon and colleagues used biometric gonioscopy to compare the anterior chamber angle on Chinese, African American, and white subjects [64]. Comparing the mean biometric gonioscopy grades for all four quadrants showed no differences by race. However, angle width decreased with increasing age, and decreased more rapidly among Chinese subjects than among the other two groups. No differences in angle findings were noted between men and women, but many of the lowest measurements were seen among older Chinese women.

A recent population-based study of eye disease from Guangzhou, China, reported that angle width was narrower in women and in older persons using both a Spaeth and Shaffer grading scheme [52].

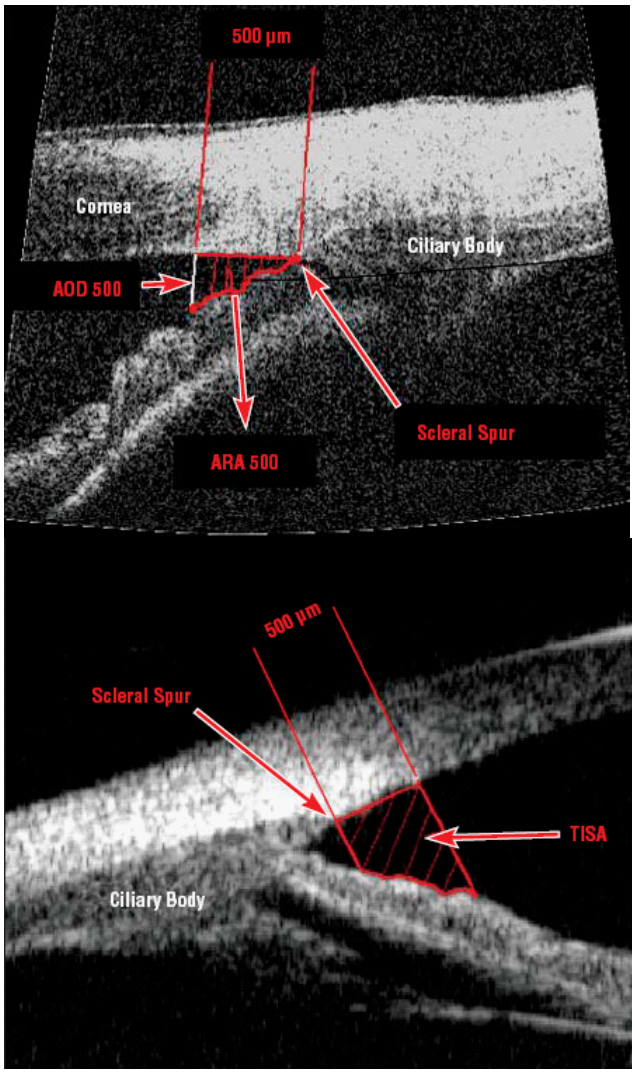

Figure 12: A, B. The ARA and the TISA are shown in the figure. Reprinted from Radhakrisnan 2005 [68] with permission of Archives of Ophthalmology.

Although there may in fact be no differences in angle configuration between men and women, it is possible that the failure of some studies to detect a sex difference is due to intra and inter-observer variability in gonioscopy.

Gonioscopy is the gold standard to diagnose the anterior chamber angle, but it is a subjective and operator dependent procedure. To define AC angle characteristics in a more objective manner several techniques have been developed. Among the mostused are UBM, Scheimpflug photography, anterior segment OCT, Eyecam, scanning peripheral anterior chamber depth analyser (SPAC).

Ultrasound Biomicroscopy (UBM)

UBM is an ultrasonic technique able to image the anterior segment. A higher ultrasound frequency compared to traditional B-scan decreases penetration but allows to obtain higher resolution images.UBM lateral and axial resolutions are about 40 and 20 microns, respectively. It's necessary that the ultrasonic waves travel through a reservoir of saline solution, generally contained in an eye cap [23].

UBM can evaluate many features of the anterior chamber. Pavlin and coll. proposed for the first time the following quantitative measurement parameters that still remain the most used [18,65,66] (Figure 11).

1. The trabecular-iris angle (TIA) is an angle measured with the apex in the iris recess and the arms of the angle passing through a point on the trabecular meshwork 500 μm from the scleral spur and the point on the iris perpendicularly opposite
2. The AOD 250/500 is calculated from the corneal endothelium to the anterior iris and measured at 250 μm (at the level of the posterior trabecular meshwork, AOD 250) or 500 μm (at the level of the anterior Schwalbe's line, AOD 500) from the scleral spur.
3. The trabecular–ciliary process distance (TCPD) is measured on a line extending from a point 500 μm anterior to the scleral spur on the corneal endothelium iris to the most anterior ciliary process passing perpendicularly through the iris.
4. The iris thickness (ID) is the iris thickness measured at 500 μm anterior to the scleral spur along the same line as the TCPD (ID1) or at 2 mm from iris root (ID2) or at the pupillary margin (ID3).
5. The iris–ciliary process distance (ICPD) is the distance between the posterior iris surface and the ciliary process along the same line as the TCPD.
6. The iris–lens contact distance (ILCD) is the contact distance between the iris at the pupillary border to the point where the anterior lens surface leaves the iris.
7. Iris zonular distance (IZD) is the distance between the iris and the zonule along the line of TCPD.
8. Iris lens angle is the angle between the iris and the lens near the pupillary edge.
9. Anterior chamber depth (ACD) is the distance measured from the corneal endothelium to the anterior lens surface.

Ishikawa and coll. proposed an alternative parameter: the angle recess area (ARA). The ARA is a triangular area bordered by the anterior iris surface, corneal endothelium and a line perpendicular to the corneal endothelium drawn to the iris surface from a point 500 μm or 750 μm anterior to the scleral spur. Instead of treating iris like a straight line as in AOD, in ARA irregularities of the iris contour are taken into account [69] (Figure 12 A).

The trabecular-iris space area (TISA) at 500 μm and 750 μm has been recently presented by Radahakrishnan to better define the filtering area compared to ARA, excluding the nonfiltering region behind the scleral spur. TISA (TISA 500 and TISA 750) is a trapezoidal area limited by: anteriorly, the AOD 500 or AOD 750 respectively; posteriorly, a line drawn from the scleral spur perpendicular to the plane of the inner scleral wall to the opposing iris; superiorly, the inner corneoscleral wall and inferiorly, the iris surface [68] (Figure 12 B).

Recently, Otori and coll. investigated the relative lens position (RLP) as a predictive parameter for appositional closure in eyes with narrow angles. RLP is calculated as follows: 10 x (ACD + 0, 5 LT)/ AL, where ACD is the anterior chamber depth, the LT the lens thickness and the AL the axial length. The first two measurements were made by UBM and the third using the IOLMaster. The RLP seems predictive of appositional closure when examined in dark conditions [70].

A good agreement between UBM and gonioscopy has been reported: the small variations could be caused by the position of the patient, who is seated during gonioscopy and in supine position while UBM is performed. Furthermore, lighting conditions can be an issue; several Authors demonstrated an improvement in agreement between UBM and gonioscopy when both examinations are performed in the same condition of light [23,71-73]. Kong and coll highlighted that on gonioscopy an appositional closure is detected everytime the TM is hidden, but it happens also if there's not physical contact (i.e. when the iris is convex and it obscures the visibility of the TM) [74].

UBM is very useful in case of corneal edema or corneal opacification that precludes gonioscopy. Secondary angle closure following post-penetrating keratoplasty glaucoma can be identified with UBM and the identification of the peripheral anterior synechiae can be useful for determining the site for subsequent glaucoma filtering surgeries or for the implantation of draining devices [66].

UBM main advantage, compared to any other optical imaging system, is its ability to view structures behind the iris, such as the ciliary body, the lens zonules and the anterior choroid. It is useful to investigate the pathogenesis of angle closure and the role of anterior rotation of the ciliary body in plateau iris, the presence of iridociliary masses, of choroidal effusions, of tilted or subluxed lens [65,75-77]. The importance of UBM in patients with plateau iris has been previously discussed.

Questions still remain about the reproducibility of UBM measurements. Tello and coll. find a high intraobserver reproducibility (coefficient of variation < 10%) but a lower interobserver reproducibility [78]. Image acquisition is responsible of this variability, but also drawing a line apart from a specific reference point can be highly subjective. Ishikawa and coll. developed a software program (UBM Pro 2000, Paradigm Medical Industries, Salt Lake City, UT, USA) to measure AOD in a semi-automated modality and they showed an improvement in reproducibility (7.3 to 2.5, coefficient of variation) [79]. Nevertheless, this program has not been diffusely used in recent studies.

Recently, as part of a population based study, the quantitative characteristics of the anterior segment with UBM have been evaluated [80]. The Authors demonstrated associations of the peripheral ACD,

location of the ciliary body and iris thickness with age, gender, refractive error, axial length and intraocular pressure. In a subsequent study [81] in a subset of patients with PAC or PAC suspects gonioscopically assesed, the Authors demonstrated that eyes with PAC/PAC suspects had shallow ACs, anteriorly located ciliary bodies, smaller angle-opening distance (AOD), smaller trabecular-iris angle (TIA) and trabecular-ciliary process distance (TCPD) and smaller dark-light changes in the peripheral AC depth, while the iris thickness was similar to that in eyes with nonoccludable angles. In particular AOD and TIA under light conditions seem to be the best UBM parameter in differentiating PAC/PAC suspects, with sensitivity of 0.82, specificity of 0.96 in PAC and sensitivity of 0.83, specificity of 0.93 in PAC suspects.

In this study, contrary to previous reports, the peripheral AC depth under light conditions could most clearly differentiate PAC/PAC suspects from nonoccludable angles. This observation is explained by the fact that dark-light changes in the AOD and TIA were significantly smaller in the PAC/PAC suspects than in the nonoccludable angles [81].

Other Authors demonstrated that UBM can be useful to evaluate the effects of Laser Peripheral Iridotomy (LPI). After LPI, UBM can demonstrate an increase of angle width and of anterior chamber depth in eyes with primary angle closure [82]. It is reported that TIA can increase after LPI in all four quadrants and AOD 250 and AOD 500 increase in the quadrant with LPI. Iris also can show morphological changes [10,83,84]. Residual angle closure after iridotomy is not infrequent: it can be observed with darkroom provocative tests and UBM in at least 1 quadrant in more than one third of cases. Following LPI, patients show lower AOD 500, ARA 750 and TIA in 4 quadrants compared to eyes without appositional angle closure [85,86]. According to Bochmann and coll, if the iridotomy is patent but small (< 100 μm) associated with residual angle closure, patient should be subjected to laser enlargement of iridotomy: in this way, AOD can be increased [87]. Cataract surgery seems to effectively resolve the residual angle closure after iridotomy, with TIA, AOD250, AOD500 and ACD increasing [88,66].

Clinical disavantages of UBM are the need of contact with the eye with potential risk of infection or corneal abrasion. The need of a saline bath makes the exam quite time consuming and discomfortable. Although UBM has given insight into the anterior chamber angle configuration and influenced the ophthalmological thinking of angle closure mechanisms, this method is limited in clinical practice by costs and by the fact that measurement of angle structures can be influenced by image acquisition and analysis. Some sources of variability can be controlled whereas others are more difficult to control and add an element of subjectivity to this technique.

Anterior Segment Optical Coherence Tomography (AS-OCT)

Anterior segment optical coherence tomography (AS-OCT) is an imaging technique that produces high-resolution cross-sectional images of the anterior segment structures. This technology uses low-coherence interferometry to measure the delay and intensity of a light beam reflected from tissue and compares it with light that has traversed a known reference path length by using a Michelson-type interferometer [89].

OCT was originally developed to acquire retinal images with 830 nm wavelength light. Using a longer wavelength light (1310 nm) the amount of scattering by the sclera and limbus can be reduced, allowing the visualization of the anterior chamber morphology with high-resolution [90].

AS-OCT devices can obtain simultaneously pachymetry maps, width and angle of the anterior chamber.

This method has a rapid acquisition and is non-contact allowing comfortable exams and avoiding mechanical distortion of the angle. A single OCT scan images the entire cornea, both angles on one meridian and the anterior portion of the lens. OCT also provides images of the iris surface and angle structures such as the scleral spur with a good resolution. These characteristics make it particularly valuable both in screening and clinical settings. Nevertheless, some angle recesses are imaged poorly compared to UBM [68] and UBM is the only technique able to image the structures behind the iris.

Different type of AS-OCT (time domain TD or spectral domain SD OCT) are commercially available (Table 6). All require only a minimal experience for image acquisition; a greater operator skill is required for the SL-OCT (Heidelberg Engineering, GmbH, Dossenheim, Germany) because it is incorporated into a modified slit-lamp biomicroscopy system that works with manual rotation of the scanning beam. AS-OCT has an high interobserver reproducibility but the measurements are not interchangeable between the different type of OCT [91,92].

Fourier Domain-OCT (or Spectral Domain-OCT) has a higher resolution and image quality than the Visante OCT (Table 7), making easier the detection of the scleral spur. SD-OCT produce larger angle width measurements compared to low resolution OCT according to Wang and coll., due to different image-processing algorithms [93,94].

Many of the UBM parameters for quantitative definition of the anterior chamber angle, like AOD or ARA, are commonly calculated also on OCT images: a significant correlation between UBM and OCT measurements has been reported [83,95]. Nevertheless studies that confront the two tecniques used different statistical methods and angle parameters, so their results are only partially comparable. For some Authors there's poor agreement between AS OCT and UBM: the first giving higher measurements than the second, but the reasons still remain unclear. It has been hypothesized that it can be due to the different calibration, to illumination condition, or to pressure of the eyecup [68,96].

AS OCT has equal [68] or higher [94] interobserver and intraobserver reproducibility than UBM. Determination of angle parameters using semiautomated software leads to variability in measurements and this is largely due to the need of manual identification of the sclera spur [96]. Using Visante OCT the scleral spur individuation is possible in approximately 70% of anterior segment images [97]. Rates of detection are worse in the superior and inferior quadrants because of the eyelids. In addition, in quadrants with a narrower anterior chamber angle, the proximity of the trabecular meshwork to the iris makes more difficult the individuation of the scleral spur [97].

Higher reproducibility can be obtained using "High-resolution Cornea" (Visante OCT) when compared to low resolution optical coherence tomography (LOCT) [94]: the easier visualization of the scleral spur (identification in 100% of images) probably accounts for this difference in reproducibility.

Wang and coll developed a specialized software to calculate anterior chamber volume (ACV) with Visante OCT, that seems to give repeatable results. Unfortunately no gold standard is available to determine ACV non-invasively [98]. Recently Fukuda compared three dimensional corneal and anterior segment OCT (CAS-OCT) and dual

scanning Scheimpflug imaging. OCT allowed obtaining the entire anterior chamber volume and the central 8 mm volume. With the dual scanning Scheimpflug only the central 8 mm olume was measured. The repeatability and reproducibility of this method was high (less than 5% variability). The 8 mm ACV measurements with CAS OCT and Scheimpflug imaging were comparable [99].

A recent study shows that Visante AS-OCT can detect angle closure in one or more quadrants in 71% of patient with clinical diagnosis of primary angle closure, while gonioscopy in 49.5% patients. The sensitivity (using gonioscopy as gold standard) was 98%, while the specificity was 55%, indicating that some subjects appeared closed on OCT but not on gonioscopy [100]. In a sample ofhealthy subjects, Sakata and coll. found that overall AS OCT tended to detect more closed angles than gonioscopy. AS OCT tended to image the temporal angles as open when gonioscopically they appeared closed, and the gonioscopist tended to see inferior and superior angles as open when the AS OCT images showed them to be closed.

The differing findings in the various quadrants may be the result of technical difficulties of performing each technique. Viewing the temporal (and nasal) angles can be difficult with gonioscopy, whereas imaging the superior and inferior quadrants with AS OCT can be difficult because of the eyelid. Furthermore, manipulations to move the lid out of the way may alter the appearance of the angle [91].

Khor and coll. also found more angle closure in superior-inferior sectors. They calculated that the inferior quadrant-only scanning protocol had the highest sensitivity for detecting angle closure (92%), but a lower specificity (54%) and had the highest AUC (area under the receiving operating characteristic curve) for detecting gonioscopic angle closure [101]. This finding is important because imaging the superior and inferior quadrants with AS OCT can be more difficult for the presence of eyelids.

The differences between gonioscopy and AS OCT could be due to variations in the iris profile due to exposure of the pupil to visible light during gonioscopy. The amount of light necessary for gonioscopy, even if small, is probably enough to open up angles that would be closed in the dark. In fact, there's a better agreement between AS-OCT with light condition and gonioscopy [100,102]. An excessive tilting of the lens during gonioscopy could be an alternative explanation.

Furthermore the two tests use different criteria to define angle closure: on gonioscopy the angle is closed when there is apposition between the iris and the posterior trabecular meshwork, whereas on AS-OCT when there is any contact between the iris and the angle structures anterior to the scleral spur [103]. An eye with low irido-TM contact just above the scleral spur which would have been labeled "open" by gonioscopy, is classified as closed on AS-OCT. In fact Sakata and coll. found the presence of low irido-TM contact in 71% of angles which resulted false positive to OCT [91].

Recently Narayanaswamy and coll in a large community based study identified the AOD 750 in the nasal and temporal area as the most useful angle measurement for identifying subjects with gonioscopically narrow angles in gradable AS-OCT images. This finding could be of relevance in view of the clinical application of AS-OCT, because in these areas the identification of angle structures is easier and more reproducible [104].

OCT proved to be very useful in case of corneal opacity that makes angle visualization gonioscopically unclear as in acute angle-closure glaucoma; images can be taken with only minimal degradation [105]. AS OCT has been used also for evaluating post-keratoplasty glaucoma, a condition in which UBM, being a contact technique, carries potential risks to the corneal graft [106].

As with UBM, OCT can demonstrate that peripheral laser iridotomy increase angle width. Recently it has been demonstrated that AOD 500, ARA500, ARA 750, TISA 500 and TISA 750 are significantly increased after LPI. In particular, the AOD500 and the TISA750 observed in light condition nearly doubled their values [106,107]. Lei and coll. evaluated also ACV, on 12 cross sectional images processed with the specialized software designed by Wang and coll, and central ACD, founding that increased in eyes subjected to iridotomy [108].

Scheimpflug Photography

Scheimpflug photography allows obtaining slit images of the anterior segment of the eye. The Topcon SL 45, the Nidek EAS-1000 and the Oculus Pentacam are non-contact devices imaging the anterior segment with the Scheimpflug method. Pentacam takes up to 50 images in 2 s and can be used to measure corneal thickness, radius and diameter of curvature, anterior chamber depth (ACD) and volume (ACV) and lens position. A dual image Scheimpflug camera (GALILEI) has recently been developed. It captures slit images from opposite sides of the illuminated slit, and averages the elevation data obtained from corresponding opposite slit images, thus potentially increasing the detection of the posterior corneal surface. The dual system requires also a shorter recording time because it can perform a complete scan (up to 60 images) in less than a second.

With the Scheimpflug systems, anterior chamber angle cannot be directly visualized because the light is unable to penetrate to the angle recess [68]: most available systems have semi-automated programs to analyze the anterior chamber angle.

Anterior chamber depth can be measured locating manually the surface of the posterior cornea and the anterior surface of crystalline lens [103,109].

The semiautomatic method to extrapolate anterior chamber angle width seems to be highly reproducible. Lam and coll. found no statistical difference between the results of two examiners: the 95% intra-observer limits of agreement were within ±5°, with ICC (intra-class correlation coefficient) below 0.75. The EAS-1000 shows also good intra-observer

OCT	IMAGE ACQUISITION SPEED	AXIAL RESOLUTION	TRANSVERSE RESOLUTION
Visante AS-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA)	2000 A-scan per second	18 µm	60 µm
Slit-lamp OCT (Heildelberg Engineering, Heildelberg, Germany)	< 2000 A-scan per second	<25 µm	20-100 µm
SD-OCT RTVue (Optovue Inc., Fremont, CA, USA) **- Cirrus HD OCT** (Carl Zeiss Meditec Inc.)	26,000 A-scans per second	5 µm	15 µm

Table 7: Main technical features of the most used OCT in commerce.

repeatability, with a 95% inter-observer limits of agreement within ±6° and an ICC around 0.75 in healthy subjects [109]. The Pentacam seems to have the same intra-observer repeatability, with relative repeatability of 5.68% for volume, 3.07% for depth and 14.41% for angle [111].

Question still remains about the validity of Scheimpflug photography for angle assessment.

In a sample of 268 persons who had participated in a population-based study of glaucoma prevalence in Singapore, reexamined by UBM, Scheimpflug photography, and gonioscopy, the data from Scheimpflug photography were generally unsatisfactory both in their variability and in their correlation with other features of these patients. The correlation with gonioscopy was fair (0.36 to 0.46) but highly nonlinear. UBM presented higher correlation coefficients with gonioscopy (0.52 to 0.59) [23]. In a more recent study on 72 eyes, the measurement of the ACA obtained with the Pentacam significantly correlated with Shaffer's grade determined by gonioscopy, but the correlation coefficient (r=0.65) was significantly lower than that obtained with UBM (r=0.90). Furthermore, there was no significant correlation between ACAmeasured with UBM and any of the Pentacam parameters in eyes with an angle width of Shaffer's grade 2 or less [112]. This discrepancy between the different methods in eyes with a narrow angle is probably due to the inability of the Pentacam to visualize the most peripheral part of the angle.

Thus, the anterior angle assessment with Pentacam, which is critically dependent on the localization of the assumed apex of the ACA, is thought to be unreliable and mostly overestimated in eyes with a narrow ACA.

The use of visible light for Scheimpflug photography could be the cause of alteration in angle width. Moreover, the Scheimpflug images are less detailed than those from the UBM, because of inability to fully visualize the entire angle. Some studies recently report a good correlation in the open-angle measurements between the Pentacam and AS-OCT, but only on a sample of healthy people [113,114].

ACD and ACV obtained with Pentacam well correlate with the ACD measured by other optical instruments, probably because they are much less dependent on the configuration of the most peripheral part of the ACA. They yield better AUC compared with the evaluation of anterior chamber angle [112,115].

EyeCam

The EyeCam™ (Clarity Medical Systems, Pleasanton, CA, USA) is a new technology derived from Retcam™ originally designed to photograph the pediatric fundus. Through the use of a lens, the device can be used to visualize the angle. This is a non-contact device and to minimize pupillary constriction the light is directed toward the angle of interest and then tilted downward (Friedman et al. 2008) [23]. The first study about Eyecam stated that this device is accurate and reliable compared to gonioscopy, but unfortunately this study did not provide any sensitivity or specificity value [116]. Another study found that the agreement between EyeCam™ and gonioscopy was good and that EyeCam™ had 76% sensitivity and 81% specificity for detecting eyes with angle closure using the two-quadrant definition of angle closure and it detected more closed angles than did gonioscopy in all quadrants [117]. In another study Baskaran et al. (2011) found that the AUC for detecting eyes with gonioscopic angle closure was similar for goniophotography and EyeCam (AUC 0.93, sensitivity= 94.7%, specificity=91.5%; P>0.95) [118]. Unfortunately there aren't studies about the comparison of the EyeCam™ and other procedures, except for gonioscopy and the few studies about this technique are all made by the same group. The device has some disadvantages: it takes longer and it is more expensive than gonioscopy and additional space is required for supine examination. It is not known if supine positioning would widen the angle due to the effect of gravity on the lens-iris diaphragm. The light source from the EyeCam™, delivered via a fiber optic cable, may cause pupil constriction, artificially altering ACA configuration. Unlike with dynamic gonioscopy, it is difficult to differentiate peripheral anterior synechiae from appositionally angle-closure, due to the inability to indent the angle.

Scanning Peripheral Anterior Chamber Depth Analyzer (SPAC)

The SPAC is a recently developed imaging device that allows assessment of the peripheral anterior chamber depth. SPAC system is an optical system; it is completely non-contact and allows quantitative measurement of ACD. It takes consecutive slit-lamp images from the optical axis of the eye to the limbus. These images are captured on a small charge-coupled device camera and are automatically analyzed by the computer. 21 measurements of the anterior chamber depth are obtained at 0.4-mm intervals and are converted into numerical and categorical grades by comparison with a normative database (obtained from a sample of Japanese subjects) [119]. It is equipped with an autofocusing system for anterior chamber depth, an automeasuring system for determining central corneal thickness and corneal radius of curvature, an autodiagnosing program for differentiating eyes with narrow angles and an autoclassifying program for categorizing eyes in subgroups according to anterior chamber depth values [120]. SPAC measurements of anterior chamber configuration correlate well with conventional methods such as Shaffer grading, van Herick grading and UBM [121]. Other studies revealed that its lower specificity in the detection of narrow angles limits its use in screening [43,122]. Wong et al. (2009) compared SL-OCT and SPAC and found that the overall sensitivity and specificity for SL-OCT were 84% and 58% vs 80% and 80% for SPAC in patients from Singapore [123]. In a recent study, Chang et al. (2011) found that, comparing SPAC, IOL-Master and AS-OCT sensitivities in detecting narrow-angle eyes were 84%, 90% and 80% respectively, while specificities were 84%, 76% and 71% [124]. This system does not image the angle directly, and therefore does not give detailed information on angle anatomy and it is not capable of detecting conditions such as peripheral anterior synechiae. Measurement at peripheral regions is also difficult for patients with prominent peripheral corneal opacity [119]. Most of the studies on SPAC have been published by a single group and assessed on a specific population (Singapore). Evidence from other groups should be warranted.

IOL-Master

The IOL-Master uses the principle of partial coherence interferometry (PCI) to measure the axial length of the globe; the anterior chamber depth is measured by optical principles using a non-PCI method. The anterior chamber depth is measured along the visual axis from the corneal epithelium to the anterior crystalline lens. The IOL-Master takes five simultaneous anterior chamber depth measurements and the mean of these five readings is used. Very few studies addressed its use in assessing anterior chamber depth and no one tried to determine sensitivity and specificity in detecting narrow angles; they rather compared ACD measured by IOL-Master to the values found by other devices. Dinc et al. found that ACD measurements obtained by the IOL Master were significantly greater compared to other devices. ACD values detected by Visante OCT and SL-OCT,

Pentacam and Orbscan IIz were not clinically interchangeable, even though no statistically significant difference was detected [125]. Lavanya et al. stated that AS-OCT gave systematically deeper anterior chamber measurements than SPAC and IOL-Master [126]. Meinhardt et al. concluded that different techniques did not vary in assessing ACD and IOL-Master showed the lowest depth values [127].

Influences on anterior chamber depth

Angle appearance can change dramatically depending on the devices and on the conditions of exam. This led to perform several provocative tests based on light-dark stimulation and on the use of drugs. As previously described, corneal indentation during gonioscopy is clinically used to discriminate between simple apposition and the presence of anterior synechiae.

When light shines on the eye the iris sphincter contracts and the peripheral iris moves centrally away from the angle. The result is in many cases a more open angle appearance [128]. Thus, the anterior chamber imaging devices can be influenced by the light used the position of the patient and other variables.

Effect of light-dark conditions

Pavlin first described a dark-room provocative test (DRPT) using UBM in eight patients who developed angle closure and appositional closure in response to decreased illumination [129]. Other authors tried to assess narrow angles through UBM under different light conditions [79,130-133]. They found a decrease in angle width in patient with narrow angles (PAC, PAC suspect, PACG or fellow eyes of persons with unilateral acute attacks) under dark-provocative condition. Barkana et al. (2007), [71] using UBM under dark and light conditions and a dark-room gonioscopy (4-mirror Zeiss-type gonioprism and a 1-mm light beam not crossing the pupillary border, avoiding a miotic response) found that therates of apposition were nearly identical at dark-room gonioscopy and dark-room UBM, and much less frequent at UBM in lighted room conditions. Sugimoto et al. [134] in Japan have published an example of gonioscopy captured using infrared light. These Authors showed substantial angle narrowing compared to standard gonioscopy with brighter illumination. Merula et al. (2008) [135] compared narrow-angle and acute glaucoma fellow eyes using UBM in light and dark condition (240 lux and 0.1 lux respectively). They didn't show any difference in angle width between these two conditions in both groups. In 2010, Wang et al. [136] showed that among eyes with narrow angles, those with the larger number of meridians with closed angles, especially in the darkroom, are more likely to have positive darkroom tests, concluding that this test may be useful in the early diagnosis of primary angle closure. Instead, Leung et al. (2007) [137] in their study concluded that the dynamic dark–light changes of the anterior chamber angle can be imaged and analyzed with anterior segment OCT and although the angle width generally decreased linearly with increasing pupil diameter, the differences of the angle width measured in the dark and in the light varied substantially among individuals. In a recent study the Authors tried to standardize the light conditions using an illuminometer (about 1400 lux for the light condition and about 3 lux for the dark condition) and the accommodation using a fixed target during the UBM measurements, and they found that the location of the ciliary body was minimally affected by dark-light changes despite substantial anterior movement of the iris root [81].

Li et al. [138] studied the response of the pupil and of the angle to 3 minutes and to 1.5 hour dark room provocative test: the anterior chamber angle configuration as measured by the number of closed angle segments did not vary significantly between baseline examination under room light conditions and that carried out at 1.5 hours of dark adaptation; in contrast, the examination of the pupil diameter and the chamber angle at 3 minutes of dark adaptation showed a significant difference from the baseline examination under room light conditions. The same group subsequently proposed a modified DRPT with an anterior chamber angle assessment by OCT at 3 minutes of dark adaptation, comparing it with a gonioscopic angle assessment after 1.5 hours, and found a higher diagnostic precision in predicting primary angle closure for the first technique (sensitivity 91% vs. 67%, specificity 57% vs. 80%) [139].

Effect of position

Supine position is needed for Eyecam™ and UBM. Only two studies try to assess the difference in ACD during prone, supine and seated position: the first found a lower depth in prone than in supine position in narrow-angle patients (but the seated position was not considered) [140]; the other one did not show any difference among prone, supine or seated position in normal subjects [141]. The anterior chamber angle width can be influenced by the intensity of the light used for examination as in Gonioscopy, SPAC, Eyecam™, OCT and Scheimpflug devices. UBM and OCT may be performed in dark conditions (AS-OCT light source provides a 0.2 lux luminosity, but this does not affect pupil diameter).

Effect of accommodation

Another variable is the quantity of accommodation: during AS-OCT and UBM measurement, accommodation is minimized by adjusting the fixation target, whereas IOL-Master, SPAC and Scheimpflug photography do not have a non-accommodative fixation target. Thus, patients undergoing evaluation by these devices may have different states of accommodation. Accommodation would be expected to lead to reduction in anterior chamber depth, and indeed the IOL-Master and SPAC tend to give shallower anterior chamber depth measurements than the AS-OCT [126].

Effect of drugs

Drug-induced angle closure is the result of: (1) crowding of the anterior chamber angle as a result of pupillary dilation, (2) pupil-block as the dilated pupil constricts or (3) idiosyncratic drug reactions that change the irido-corneal angle by formation of cilio-choroidal effusions. These drugs can also create different basal pupil dilation and alter the ACA (anterior chamber angle) assessment.UBM has been used to evaluate the effects of drugs on anterior chamber angle, iris, and ciliary body. Angle opening is increased after pilocarpine installation in eyes with narrow angle, whereas angle opening is decreased in eyes with a wide or normal angle [142-144]. Hung assessed normal subjects using Scheimpflug photography and found narrowed angles after 2% and 4% pilocarpine instillation [145,146]. Kobayashi compared the UBM response to 2% pilocarpine of narrow angle patients to normal controls and reported the same results [147]. Friedman and colleagues reported variable angle responses to the administration of 4% pilocarpine [130]. Most of these studies are performed on Asian population, thus it remains unclear if the effect of pilocarpine on ACA configuration can vary by race, or if differences in study methodology caused variable responses. Many other drugs can influence the anterior chamber angle, such as Bronchodilators, Antidepressants, Anticholinergics, General Anaesthetics, Cough Suppressants, Recreational Drugs, Botulinum Toxin, Sympathomimetics and Poisons (like Belladonna). Adrenaline and stress can also change the configuration of the angle [128].

Effect of corneal indentation

Matsunaga et al. (2004) [148] assessed the UBM changes in the ACA when indenting the central cornea; they used a modified eyecup that places pressure on the central cornea and demonstrated that the angle widened in all subgroups (narrow angles, PAS in the angle and plateau configuration) but particularly in the narrow angles without PAS and plateau iris. Prata et al. (2010) [149] tried an indentation SL-OCT technique to assess the angle configuration. They were able not only to view the angle configuration but also to differentiate appositional and synechial angle closure in eyes with iridotrabecular contact.

Conclusions

The closed angle configuration is a diffuse condition especially in Asian countries and can lead to blinding complications in a large number of individuals. Although this anatomical variation had been diffusely known for many years and diffusely described, the cut-off to start treatment is largely arbitrary.

Gonioscopy is the current reference standard for assessing ACA structures and configuration and is an invaluable technique in primary eye care. Definitions of angle findings vary across grading schemes, and no single scheme is used, although the Shaffer angle width appears to be commonly reported in research. Gonioscopy is prone to potential measurement errors including artificially opening or closing the angle due to how the lens is placed on the eye. Reproducibility of gonioscopy has only rarely been studied in small samples of patients, with moderate agreement reported.

However, based on accumulating evidence in the literature that appositional closure may be harmful to trabecular function, and associations now found between degree of angle opening and the prevalence of PAS and elevated IOP, there appears to be an increasing belief that the term "occludable" should apply to angles with 180 degrees of appositional closure as opposed to the previous definition of 270 degrees [150]. Some have argued that any appositional closure is pathologic, but this remains controversial.

Although this is a good and acceptable clinical definition, the lack of longitudinal studies implies that this cut-off is arbitrary.

In recent years several new device to evaluate the anterior chamber angle have been developed and some of them have been diffusely investigated.

Different parameters useful for identifying the risk of appositional closure have been described for each device and each technology has its advantages and disadvantages. Ultrasound methods are less dependent on light and accommodation and can provide informations on the structures behind the iris, but they require contact and a skilled operator.

Optical methods are non contact, fast but some of them can be influenced by accommodation or illumination. They also are limited because it is difficult or impossible to detect the presence of posterior synechiae. Furthermore all the newer techniques use different references compared to gonioscopy. So far sensitivity, specificity and area under the curve are likely not to be the best way of analyzing the performance of any new device in the absence of a clear reference standard. Furthermore some of the studies presented in this review are not population based and the oversampling of subjects with narrow angles may severely hinder the results. Longitudinal studies would be required to determine wheter eyes classified as closed are at risk of developing complications. Nevertheless this approach may be difficult to fulfill due to practical and ethical reasons.

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