

AQUEOUS HUMOR DYNAMICS

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I. ANATOMY

LIMBUS

Transition zone between the cornea and sclera

Internal indentation, or scleral sulcus, houses meshwork structures and serves as the principal site of aqueous outflow

A. Schwalbe's Line

Termination of Descemet's membrane and clinically, the corneal optical wedge, or parallelopiped (junction of Bowman's and Descemet's membranes)
AKA Zone S (50-150 microns)

Subdivisions:

- Anterior border - transition from trabecular to corneal endothelium and the termination of Descemet's membrane
- Posterior border - elevation formed by the oblique insertion of uveal trabeculae into limbal stroma

B. Trabecular Meshwork

Three dimensional set of diagonally-crossing collagen fibers

Contained within the scleral sulcus, converting the latter into a circular channel, Schlemm's canal

Consists of a connective tissue core surrounded by endothelium and may be subdivided into three portions:

- (1) Uveal meshwork - adjacent to the aqueous in the anterior chamber; formed of trabecular bands with irregular 25 - 75 micron openings extending from the iris root and ciliary body to Schwalbe's line. Each trabecular band or sheet in the uveal and corneoscleral meshwork

is composed of a connective tissue core surrounded by elastic fibers, a glass membrane, and trabecular endothelium

- (2) Corneoscleral meshwork - sheets of trabeculae with elliptical openings ranging from 5 - 50 microns in diameter extending from the scleral spur to the anterior scleral sulcus
- (3) Juxtacanalicular connective tissue - outermost portion of trabecular meshwork composed of a connective tissue core lined on either side by endothelium. Outer endothelial layer is continuous with the inner wall of Schlemm's canal and may be the site accounting for the major resistance to aqueous outflow. A transcellular aqueous transport system consisting of pores and giant vacuoles may provide communication with Schlemm's canal. Aqueous subsequently flows distally to:
- (4) Schlemm's canal - an endothelial-lined channel averaging 190-370 microns in diameter.
Pressure-dependent changes in aqueous outflow such as increased resistance to aqueous outflow with elevation of intraocular pressure may be secondary to a collapse of Schlemm's canal
- (5) Intrasccleral collector channels - direct and indirect systems including aqueous veins of Ascher
- (6) Episcleral and conjunctival veins
- (7) Episcleral veins drain to anterior ciliary and superior ophthalmic veins => cavernous sinus.
Conjunctival veins drain to palpebral and angular veins => superior ophthalmic or facial veins.
- (8) Cavernous sinus
 - C. Scleral spur- posterior margin of scleral sulcus formed by the insertion of the longitudinal ciliary muscle fibers. Composed primarily of collagen (75-80%)
 - D. Ciliary Body - extends 6 mm. from the scleral spur and posterior pigment epithelium of the iris anteriorly to the retina and choroid at the ora serrata posteriorly. Composed of muscle, blood vessels and epithelia. Ciliary body band represents anterior aspect of ciliary

body visible on gonioscopy. Width of ciliary body band depends on level of iris insertion

I. PARS PLICATA - Anterior 2 mm.

1. Ciliary muscle

- a. Longitudinal fibers - insert into scleral spur anteriorly (attaching ciliary body to limbus) and suprachoroidal lamina posteriorly as far back as equator or beyond; affect outflow facility
- b. Circular fibers - occupy anterior and inner portion of ciliary muscle, are oriented parallel to the limbus, and influence accommodation
- c. Radial fibers - connect a. and b.

2. Ciliary vessels - branches of the anterior ciliary and two long posterior ciliary arteries anastomose near iris root to form the major arterial circle supplying the iris, ciliary body, and choroid; disrupted by iridodialyses and in some hyphemas. Venous drainage occurs through the vortex system, intrascleral venous plexus, and episcleral veins

3. Ciliary processes (approximately 70) - radial folds in pars plicata. Zonular fibers attach primarily in the valleys of the ciliary processes and also along the pars plana

a. Ciliary epithelium:

1. Pigmented - comprises outer layer, adjacent to stroma, and composed of low cuboidal cells with multiple basal infoldings, a large nucleus, and melanosomes
2. Nonpigmented - inner layer, adjacent to aqueous in the posterior chamber, consisting of columnar cells (cuboidal in pars plana). Intercellular tight junctions (zonulae occludens) form major element of blood-aqueous barrier. Tips or crests of nonpigmented ciliary epithelia are site of active secretion, hence numerous mitochondria, rough endoplasmic reticulum, pinocytotic

vesicles, Na-K activated ATPase and carbonic anhydrase

- b. Capillaries- network comprises core of each process; extremely high rate of blood flow from major arterial circle. Surrounding endothelium with fenestrae and hence increased permeability
- c. Stroma- mucopolysaccharide ground substance and collagen separating capillary network from epithelial layers

II. PARS PLANA - posterior 4 mm. of ciliary body, joining the choroid and ora serrata; lined by pigmented and nonpigmented epithelial layers. The non-pigmented epithelial cells produce the acid mucopolysaccharide component of the vitreous

E. Iris - inserts into anterior aspect of ciliary body; the variable insertion of the peripheral iris into the ciliary body determines the clinical appearance of the ciliary body band. The iris approach may be flat, plateau, convex, or concave

II. PHYSIOLOGY

CILIARY BODY FUNCTIONS:

1. Suspend crystalline lens and alter its shape:
 - a. Accommodation and miotics - stimulate ciliary muscles inducing anterior lens movement and an increased A-P lens diameter, shallowing the anterior chamber
 - b. Cycloplegics - induce relaxation of the ciliary muscles, tightening the zonules and resulting in posterior lens movement and decreased A-P lens diameter, deepening the anterior chamber
 - c. Effects on relative pupillary block may also influence central and peripheral anterior chamber depth

2. Formation of aqueous humor:

Aqueous is derived from plasma within the capillary network of the ciliary processes by three mechanisms:

- a. Diffusion - lipid-soluble substances are transported through the lipid portions of the cell membrane proportional to a concentration gradient across the membrane
- b. Ultrafiltration - water and water-soluble substances, limited by size and charge, flow through theoretical micropores in the cell membrane in response to an osmotic gradient or hydrostatic pressure; influenced by intraocular pressure, blood pressure in the ciliary capillaries, and plasma oncotic pressure

Note: Diffusion and ultrafiltration are both passive mechanisms, with lipid- and water-soluble substances from the capillary core traversing the stroma and passing between pigmented epithelial cells and limited by the tight junctions of the non-pigmented epithelial cells

- c. Active transport (secretion) - water-soluble substances of larger size or greater charge are actively transported across the cell membrane, requiring the expenditure of energy; Na-K ATPase and glycolytic enzymes are present in nonpigmented epithelial cells. Active transport is decreased by hypoxia, hypothermia, and any inhibitor of active metabolism. Active transport accounts for the majority of aqueous production.

Rate of aqueous Humor Formation: 2.0 - 3.0 microliters/min.

Volume of Anterior Chamber	250 microliters
Volume of Posterior Chamber	60 microliters
Turnover of aqueous:	1.5 - 2 hours

- 3. Aqueous humor formation decreases with sleep (suppression of 45±20%), advancing age(decrease of 2% per decade), uveitis, RD, and ciliochoroidal detachment. Decreased aqueous humor formation with increased IOP (pseudofacility) has been disputed by recent studies indicating that rate of aqueous formation is relatively pressure-insensitive (Shields, 1992)
- 1. Uveoscleral outflow - second major route of aqueous drainage through the face of the ciliary body and iris root to the ciliary muscle and suprachoroidal space to either veins in the ciliary body, choroid, and sclera or through scleral pores to episcleral tissue; accounts for an estimated 20% of total outflow. Increased by cycloplegics, epinephrine, and cyclodialysis; decreased by miotics. Uveoscleral outflow is relatively pressure independent

although reportedly may improve with IOP elevation, presumably due to ultrafiltration of aqueous into uveal vessels

5. Uveovortex outflow - tracer substances have also been demonstrated to traverse vessels of the iris, ciliary muscle, and anterior choroid, eventually reaching the vortex veins
6. Formation of acid mucopolysaccharide component of the vitreous which enters the vitreous cavity at the vitreous base
7. Alter facility of outflow:
 - Contraction of ciliary muscles (e.g., parasympathomimetics) increases trabecular outflow and decreases uveoscleral outflow
 - Relaxation of ciliary muscles (e.g., cycloplegics) decreases trabecular outflow and increases uveoscleral outflow

8. Composition of Aqueous Humor

Relative to plasma, aqueous humor has a:

- Slight hypertonicity and acidity (pH 7.2 in AC)
- **Marked excess of ascorbate (15 times greater than arterial plasma)**
- Marked deficit of protein (0.02% in aqueous vs. 7% in plasma)
- Slight excess of chloride and lactic acid
- Slight deficit of sodium, bicarbonate, carbon dioxide, and glucose
- Protein and antibodies in aqueous equilibrate with those in serum when a plasmoid aqueous occurs with an anterior uveitis
- Albumin/globulin ratio is similar to plasma, although there is less gamma globulin

9. Function of Aqueous Humor:

Maintain intraocular pressure

Provide substrates (glucose, oxygen, electrolytes) for metabolic requirements of avascular cornea and lens

Remove metabolic products (lactate, pyruvate, carbon dioxide)

Possible role in metabolism of vitreous and retina

III. INTRAOCULAR PRESSURE

- "Normal" IOP - that pressure which does not result in glaucomatous damage.
- "Average" IOP - 15.8 mm Hg with Schiötz tonometry
 - 16 mm Hg with applanation tonometry
- IOP distribution not strictly Gaussian with skew toward higher IOP
- Standard deviation(SD) for IOP approximately 2.5 mm Hg:
 - 2 SD places 95% of a Gaussian distribution below 21 mmHg
- Interpretation of 21 mmHg as the "upper limit of normal" incorrect as IOP distribution not entirely Gaussian but skewed
- Factors influencing IOP:
 - Genetics - probable polygenic, multifactorial mode
 - Age - Probable increased IOP with advancing age
 - Sex - Equivalent IOP over age interval 2&-40 years, then mean IOP greater in females
 - Refractive error - possible correlation between increased IOP and increasing axial lengths and myopia
 - Race - slightly higher IOP in black versus white patients
 - Diurnal variation - possibly related to plasma cortisol level:
 - peak IOP often in morning though considerable variation
 - Postural influence - increasing IOP from sitting to supine to feet elevation to head inversion, greatest in glaucomatous eyes
 - Valsalva maneuver - may elevate IOP, possibly by increasing episcleral venous pressure
 - Blinking and lid squeezing - mild to marked IOP elevation

IV. TONOMETRY

Definition: Measurement of the IOP by relating a deformation of the globe to the force responsible for the deformation

A. INDENTATION TONOMETRY

- Prototype Schiötz tonometer

- Schiøtz footplate rests on cornea while plunger of known weight indents cornea to a degree indicated by movement of needle on scale
- Corneal deformation produces a truncated cone
- Indentation technique raises IOP to P_t from P_o . The estimate of P_o is dependent upon ocular rigidity (k)
- A low ocular rigidity (k) yields a falsely low IOP reading. Potential etiologies include:
 - High myopia, miotic therapy (especially cholinesterase inhibitors), previous intraocular surgery (including retinal detachment and vitrectomy surgery and cataract extraction), vasodilator therapy, intravitreal injection of a compressible gas, osteogenesis imperfecta, and thyroid disease
- A high ocular rigidity (k) yields a falsely high IOP reading. Potential etiologies include:
 - High hyperopia and vasoconstrictor therapy
- Other potential causes of error:
 - Blood volume alterations (expulsion of intraocular blood during indentation)
 - Corneal factors - steeper or thicker corneas may displace more fluid on indentation, resulting in falsely high IOP measurements
 - Moses effect - cornea may mold into space between plunger and hole in tonometer footplate, pushing up plunger and yielding a falsely high IOP reading

B. APPLANATION TONOMETRY

- Prototype Goldmann tonometer
- Based upon modification of the Imbert-Fick law for ideal, thin-walled spheres:

$$P_t = W/A \Rightarrow W = P_t \times A$$

W = External force against sphere

P_t = Pressure within sphere

A = Area flattened (applanated) by external force

- Assumptions - object perfectly spherical, dry, perfectly flexible, and infinitely thin

- Modified Imbert-Fick Law:

$$W + S = P_t \times A + B$$

S = Surface tension

B = Force required to bend cornea

- When A = 7.35 mm² or the diameter of external corneal applanation = 3.06 mm, then

$$S = B \text{ and } W = P_t$$

Force of cornea resisting flattening cancels out capillary attraction of tear meniscus pulling tonometer to eye when diameter of applanating head = 3.06 mm

- Small aqueous volume ($\approx 0.5 \text{ mm}^3$) is displaced with applanation so P_t approximates P_o and ocular rigidity (k) does not affect reading significantly

- Sources of error:

- Falsely high IOP reading - wide or vertically misaligned mires, thick corneas (increased collagen), marked astigmatism (increase of 1 mm Hg per 3 diopter increase in corneal power), lid squeezing, breath holding, tight collars or Valsalva maneuvers, or excess extraocular muscle force applied to a restricted globe
- Falsely low IOP reading - applanation without fluorescein, corneal edema, prolonged corneal contact

- Marked corneal astigmatism - average vertical and horizontal applanating head readings or orient red line on Goldmann tonometer prism holder to least curved meridian of cornea (along negative axis of ellipse)

- Other applanation tonometers with variable force:

- Perkins - hand-held, similar to Goldmann
- Draeger - electric motor varies force
- Mackay-Marg - measures force required to keep flat plate of plunger flush with sleeve against pressure of corneal deformation; sleeve compensates for force required to bend cornea. Readings statistically higher than Goldmann tonometry. Accurate tonometer in eyes with irregular corneas. Several newer tonometers utilize Mackay-Marg principles, including, the Tono-Pen

- Tono-Pen - probe indents cornea; microprocessor determines IOP and statistical reliability
 - Pneumatic tonometer - air pressure sensor measures IOP as corneal deformation transferred to surrounding structures; readings statistically higher than Goldmann tonometry
- Disinfection of applanation tips (immediately after use):
 - Thoroughly wipe with 70% isopropyl alcohol swab or 70% ethanol
 - Soak in 70% isopropyl alcohol solution for 5 minutes
 - Allow alcohol to evaporate or dry prism head to prevent corneal epithelial toxicity
 - Soak in a 1:10 sodium hypochlorite (household bleach) or 3% hydrogen peroxide solution for 5 minutes. Follow by rinsing and drying to prevent damage to corneal epithelium

C. NON-CONTACT TONOMETRY

- Concept - puff of room air deforms cornea with constant force
 - Time from internal reference point to central corneal flattening (maximum light detection) is directly related to force required and is converted to IOP (via calibrations with Goldmann tonometry) and displayed on digital readout
- Average time interval during measurements is 1 - 3 milliseconds, or approximately 1/500 of a cardiac cycle; instantaneous fluctuations may thus occur. Recommend that at least three readings be averaged to improve accuracy.
- Reasonable correlation with Goldmann tonometry within normal IOP range; decreased reliability with higher IOP levels.

D. CONSTANT FORCE APPLANATION TONOMETRY

- Maklakov tonometer - IOP determined by measuring the area of the cornea flattened by a known weight.

V. TONOGRAPHY

- A means of determining aqueous outflow

- Schiøtz tonometer is placed on cornea elevating the IOP and causing an increased rate of aqueous outflow and a gradual reduction in IOP

$$F = C (P_o - P_v) \quad \text{or} \quad P_o = F/C + P_v$$

F Rate of aqueous outflow

C Coefficient of outflow facility

P_o Baseline IOP

P_v Episcleral venous pressure (EVP)

- Outflow facility = Rate of loss of aqueous per mm Hg of raised IOP per minute
- Total outflow facility = C value = True outflow facility + Pseudo facility (decreased aqueous production with elevated IOP creating impression of increased outflow; controversial)
- C averages 0.28 microliters / min / mmHg (abnormal C < 0.20)
- Given elevation in P_v produces corresponding increase in P_o
- Sources of error with tonography:
 - Increased resistance to aqueous outflow with increased IOP
 - Increased episcleral venous pressure with increased IOP
 - Effects of ocular rigidity and expulsion of uveal blood
 - Instrument calibration, patient cooperation

VI. GONIOSCOPY

- Clinical technique of visualizing AC angle structures for diagnostic and therapeutic purposes
- Direct visualization precluded by the phenomenon of total internal reflection at the cornea-air interface since light rays emanating from the AC exceed the critical angle for the cornea-air interface (approximately 46°)
- Goniolens, with index of refraction (n) similar to cornea, eliminates the optical effect of the anterior corneal surface and light rays from the AC enter the contact lens

- Light rays pass from the contact lens-air interface by two basic designs:
 - Direct gonioscopy - goniolens refracts rays at lens-air interface (e.g., Koepe and Barkan goniolenses); external light source and supine patient required
 - Indirect gonioscopy - light rays reflected by mirror in goniolens (e.g., Goldmann, Zeiss). Indentation gonioscopes (Zeiss, Posner) enable one to distinguish appositional versus synechial angle-closure

VII. MANOMETRY

- Definition - the measurement of episcleral venous pressure (EVP)
- Manometer - a hollow applanating head filled with air or saline with a thin overlying membrane. Pressure within head is increased until collapse of underlying episcleral vein is achieved
- Normal episcleral venous pressure: 8-12 mm Hg
- Elevation in EVP results in 1:1 increase in IOP in acute setting; chronic EVP elevations may result in more complex changes in IOP

THE OPTIC NERVE

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THE OPTIC NERVE

- Second cranial nerve
- Contains approximately 1.2 million axons although considerable variation exists ($\pm 200,000$ nerve fibers)
- Axon cell bodies constitute the ganglion cells of the retina
 - Axons converge upon the optic nerve from all points in the retina
 - At surface of optic nerve, axons bend acutely and exit the globe through the fenestrated scleral canal (lamina cribrosa)
 - Axons follow visual pathway from the optic nerve to the optic chiasm and optic tract to synapse in the lateral geniculate body of the thalamus en route to the optic radiations and subsequently the occipital cortex
- Normal and Glaucomatous Optic Nerve Head
 - Optic nerve head connotes the three-dimensional distal portion of the optic nerve
 - Usually vertically ovoid in shape
 - Extends from the retinal surface to the lamina cribrosa sclera
 - Represents site of exit of all retinal ganglion cell axons
 - Located 3 to 4 mm nasal to the fovea
 - Composed of neural tissue, glial and collagenous supportive tissue, and blood vessels
 - Approximately 1.5 mm in diameter (considerable variation)
 - Reported sixfold difference in area of normal nerve heads
 - Central portion of the nerve generally contains a depression, the cup, representing a partial or complete absence of axons

- Tissue between the cup and disc margins comprises the neural rim
- Loss of axonal bundles leads to neural rim changes of glaucomatous optic atrophy and visible defects in the retinal NFL
- Alterations in neural rim of glaucomatous eye causes cup enlargement and VF loss
- Cup:disc ratio (C/D) an indirect measure of neuroretinal rim and may be misleading
 - Increased nerve head diameter may be associated with an enlarged cup and decreased neural rim width despite a normal amount of neural tissue (neuroretinal rim area)
- Neural rim of normal optic nerve typically broadest in the inferior quadrant, followed by the superior and then nasal rims, with the temporal rim being the thinnest
 - Stereoscopic studies of normal eyes reveal a mean C/D of 0.4 with only approximately 5% of eyes ≥ 0.7
 - C/D difference of > 0.2 between fellow eyes occurs in only 1% of the normal population
 - Size of physiologic cups may reflect polygenic multifactorial inheritance
 - Racial differences reveal a larger disc and C/D in black versus white patients
 - Glaucomatous optic atrophy characterized by a progressive, asymmetric loss of neural rim tissue

• Since there are no photoreceptors overlying the optic nerve head, it is projected into space as a 5-7 degree absolute scotoma, the blind spot (of Mariotte), in the temporal visual field

• Divisions of the optic nerve head and vasculature:

- a. Nerve fiber layer- superficial retinal nerve fibers enter the optic nerve in characteristic distribution which account for glaucomatous nerve fiber bundle and subsequent visual field defects. Nerve fibers from the temporal periphery originate on either side of a horizontal dividing line, the median raphe, and arch superior or inferior to the fovea as arcuate fibers. Arcuate nerve fibers entering the superior and inferior poles of the nerve may be more susceptible to glaucomatous damage. Nerve fibers

from the central retina, the papillomacular fibers, and nasal fibers follow a more direct path to the optic nerve. Nerve fibers may be visible ophthalmoscopically as retinal striations. Nerve fiber layer is supported by astrocytes and receives its vascular supply primarily by the arteriolar branches of the central retinal artery

- b. Prelaminar region- clinically visible as the central cup, this region is composed of axons with an increase in astroglial supportive tissue. Vascular supply primarily via short posterior ciliary arteries and possibly indirect branches of peripapillary choroid
 - c. Lamina cribrosa region- fenestrated sheets of scleral connective tissue stacked in approximately 10 plates with 200 - 1,000 fenestrae permitting bundles, or fascicles, of neurons to exit. Vascular supply derived from the short posterior ciliary arteries which form the vascular circle of Zinn-Haller
 - d. Retrolaminar region- posterior to the lamina, this extraocular region is characterized by the acquisition of myelin produced by oligodendrocytes, thereby doubling the diameter of the nerve. Vascular supply is derived from branches of the meningeal and centrifugal branches of the central retinal artery (both ciliary and retinal circulations)
- Theories of glaucomatous optic atrophy:
 - Mechanical- elevation of intraocular pressure leads to inhibition of orthograde and retrograde axonal transport at the lamina cribrosa as well as axonal compression with subsequent compromise
 1. Vascular- ischemia on the basis of intraocular pressure elevation or unrelated vascular disease leads to obstruction of axoplasmic flow and axonal loss
 2. Mechanical and vascular factors may coexist
 - Histology of glaucomatous optic atrophy:
 - Loss of optic nerve neuroretinal rim (cup enlargement) results primarily from loss of axons and to a lesser extent, changes in capillaries and glial tissue

- Tissue loss begins at the lamina cribrosa and is accompanied by compaction and fusion of the laminar plates
- Greater than 20 - 35% of axons may be lost prior to detectable visual field loss
- Axonal loss may be generalized, but is often concentrated at the superior and inferior optic nerve where axon density is greatest
- Larger diameter nerve fibers, located in higher proportion in the inferior and superior poles, are inherently more susceptible to glaucomatous damage
- Glaucomatous cupping in infants and children may be somewhat reversible due to an expansile scleral ring
- In advanced glaucoma, collapse of the laminar plates may be followed by a posterior bowing of the lamina
- Schnabel's cavernous atrophy - atrophy of neural elements creating empty cystic spaces which stain positive for acid mucopolysaccharides (AMP) including hyaluronic acid
 - Reported to occur following severe IOP elevations and possibly in setting of normal IOP's as an involutinal change associated with atherosclerosis

•Morphology of Glaucomatous Optic Atrophy:

I. Focal signs

- Focal enlargement of cup (focal atrophy or notching of the neuroretinal rim)
- Nerve fiber layer defects (localized or diffuse)
- Regional Pallor / Cup discrepancy (glaucomatous cupping may precede increased pallor)
- Optic nerve nerve fiber layer hemorrhage (association also with low tension glaucoma)
- "Saucerization" to optic nerve rim margin
- Vertical elongation of the cup
- Progressive localized loss of neuroretinal rim

II. Generalized signs

- Enlarged cup to disc ratio
- Asymmetry of optic nerve head cupping
- Progressive concentric enlargement of cup

III. Less specific signs

- Exposure of the lamina cribrosa (increased depth of cupping)
- Nasal displacement of the retinal vessels

- Baring of circumlinear vessels (vessels do not curve to outline cup but are 'bared' from its margin)
- Peripapillary atrophy (halo)

Note: Optic nerve changes precede visual field changes in most patients. Optic nerve head evaluation must be performed stereoscopically to appreciate subtleties of contour and optimally documented by stereophotography or similar means

- Susceptibility to Glaucomatous Damage
 - Level of IOP
 - Advancing age
 - Cardiovascular disease
 - Heredity
 - Size of scleral canal
 - Diabetes mellitus
 - Myopia
 - Race
- Reversibility of Glaucomatous Cupping
 - Most common in infants and children, especially during first year of life when IOP reduced surgically
 - Reported reversal of glaucomatous cupping and VF loss in adults controversial. May occur with early onset of glaucomatous atrophy following substantial IOP reduction medically or surgically