PATHOPHYSIOLOGY OF GLAUCOMA

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AQUEOUS HUMOR DYNAMICS

The clear intraocular fluid called aqueous humor (AH) is produced by the ciliary body and is secreted into the posterior chamber. The three green arrows in Figure 9.1 indicate the 'aqueous humor inflow' pathway.

The aqueous humor bathes and nourishes the crystalline lens and then circulates into the anterior chamber (enclosed by the cornea) through the pupil (indicated by the single green arrow going across the iris in Figure 9.1). The aqueous humor leaves the eye through the trabecular meshwork and into Schlemm's canal ('trabecular outflow') and through the peripheral base of the iris, into the ciliary body, and through the sclera ('uveoscleral outflow).

- Approximately 15% of the AH diffuses through the iris stroma
- Blood-aqueous barrier: Non-pigmented epithelium of ciliary body and Iris stroma

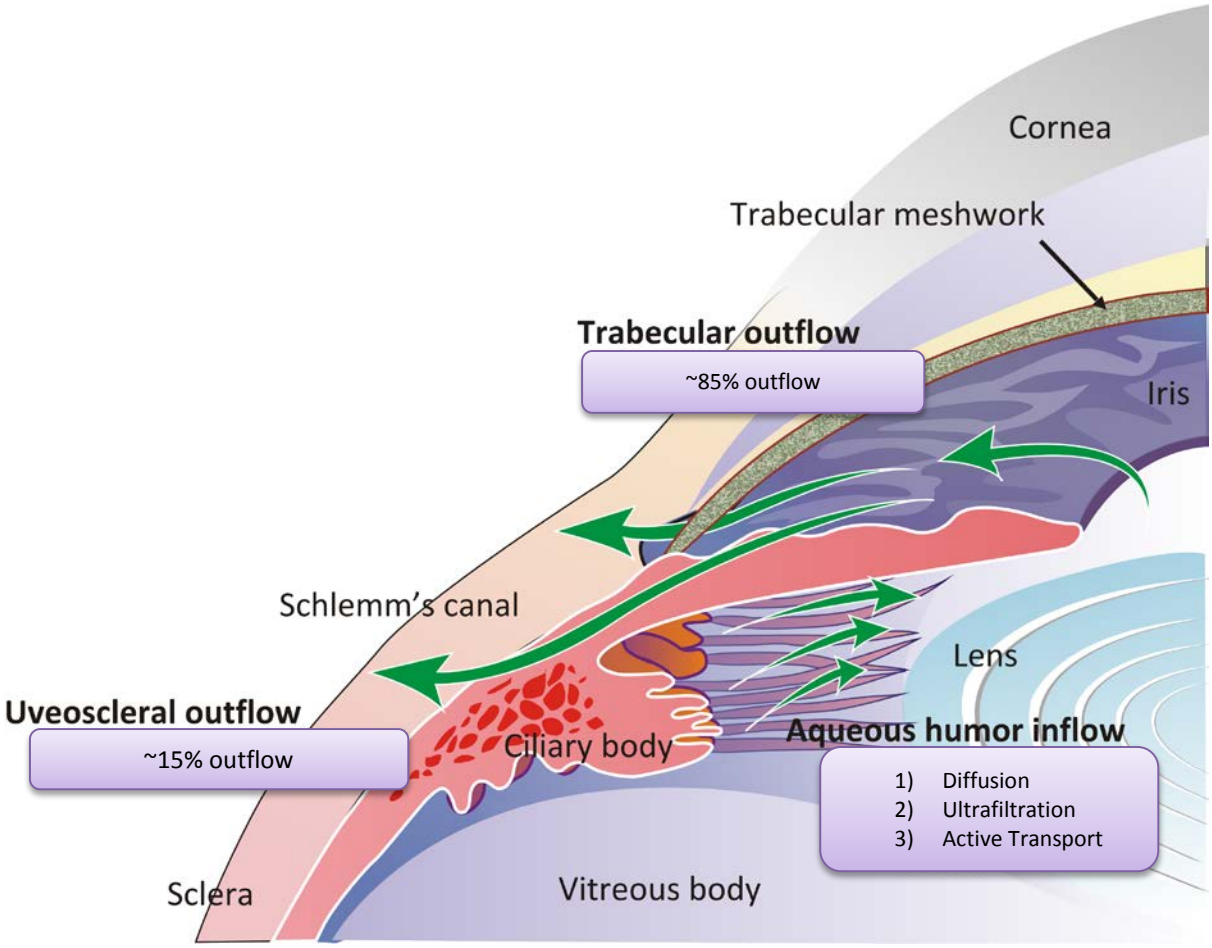


Figure 9.1: *Aqueous humor production and flow path*

AQUEOUS HUMOR DYNAMICS – INFLOW VERSUS OUTFLOW

The production of aqueous humor inside the eye (the inflow) and its removal from the eye (the outflow) are major components of maintaining a stable intraocular pressure.

- Aqueous humor is produced at the rate of about 2.4 uL/minute.

Under steady state conditions, the inflow of aqueous humor is equal to the outflow. The balance between the inflow and outflow results in a measureable intraocular pressure (IOP).

There is a diurnal variation in the production of the aqueous humor, which results in a variation of the IOP over the course of the day. The IOP is usually found to be highest in the morning and lowest in the evening.

AQUEOUS HUMOR – INFLOW

The following factors play important roles in secretion of the aqueous humor:

1) Diffusion
2) Ultrafiltration
3) Active Transport
   a. Na/K/ATPase
   b. Carbonic anhydrase

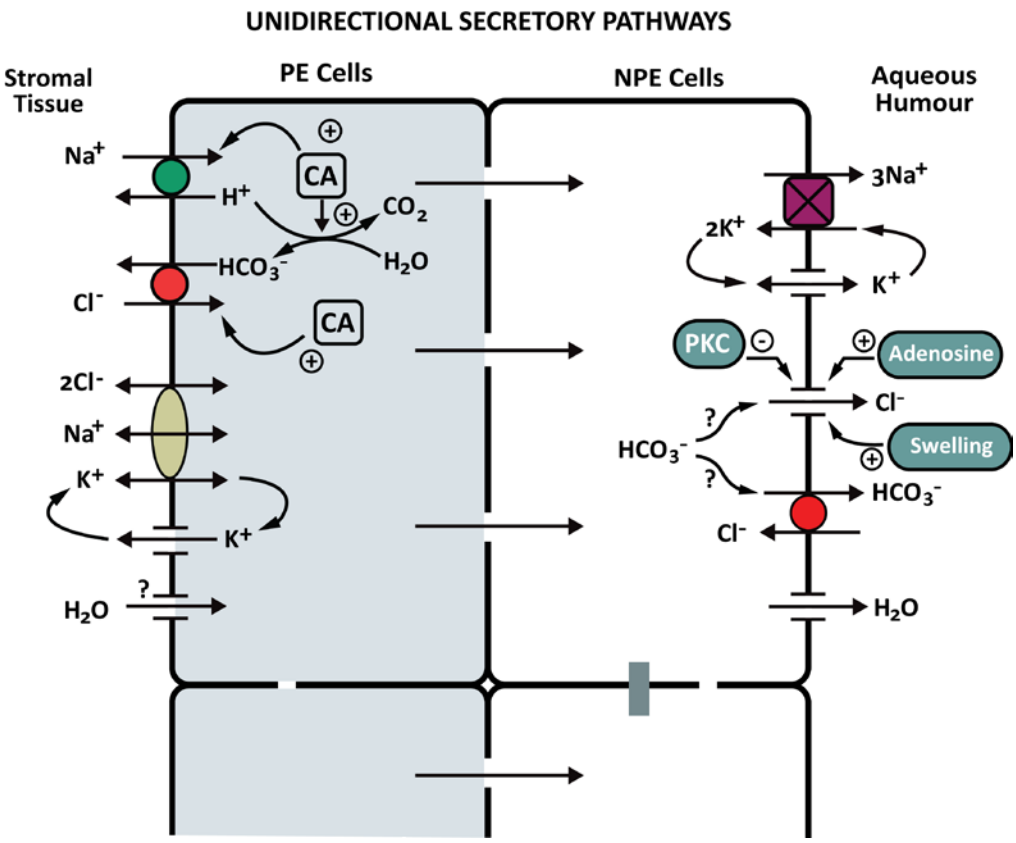


Figure 9.2: *Secretory pathways for the production of aqueous humor*

Definitions of the components of the aqueous humor production process are as follows:

Diffusion – passive movement of solutes, from the stromal vessels, over a concentration gradient.

Ultra-filtration – passive movement of water and water soluble substances across cell membrane in response to different hydrostatic pressures in the blood and osmotic pressure.

Active Transport – energy dependent mechanism responsible for moving solutes against a pressure gradient and cell membrane. Na/K/ATPase pumps sodium out of the non-pigmented epithelium and into the aqueous humor channels to create hyperosmotic environment to draw water out. Carbonic anhydrase is moved out with Sodium (Na) to further enhance the passive flow of water.

AQUEOUS HUMOR OUTFLOW

Approximately 85% of the aqueous humor outflow takes place through the trabecular meshwork. The major features of the aqueous humor drainage system are shown in Figure 9.3 and are as follows:

SCHLEMM'S CANAL

- Forms outer boundary of endothelial meshwork
- Inner wall contains vacuoles to transport AH into canal
- Collector channels emerge from outer wall and pass directly into the episcleral venous plexus

UVEAL MESHWORK (INNERMOST)

- Collagen and elastin beams
- Open spaces between beams

CORNEOSCLERAL MESHWORK

- Contain lamella with single layer of endothelial trabecular cells
- Capable of phagocytosis and tissue repair

JUXTACANALICULAR (OUTERMOST)

- Formed by endothelial cells lining inner wall of Schlemm's canal and develop pores, vacuoles and channels for aqueous to pass through

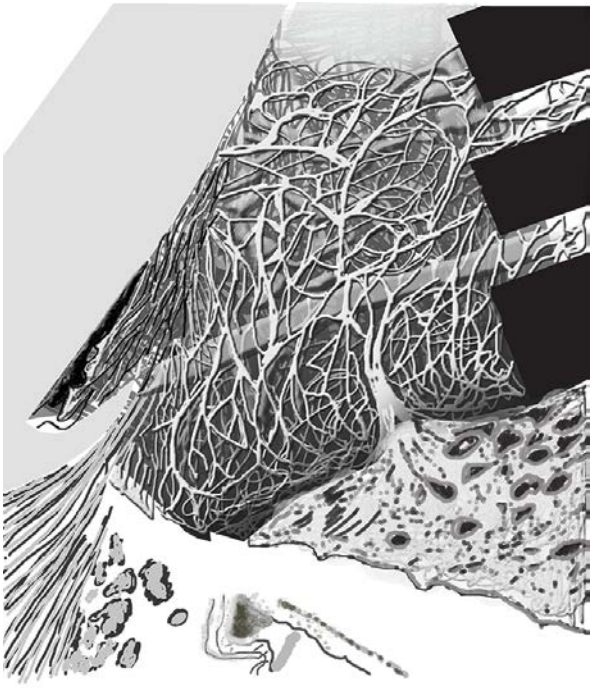


Figure 9.3: *Anatomy of the anterior chamber angle drainage system*

INCREASE IN RESISTANCE OF OUTFLOW CAUSES IOP RISE

An increase in resistance to aqueous humor outflow through the trabecular meshwork (TM) may occur due to normal age-related changes or may be associated with glaucoma.

The normal aging changes are as follows:

- Loss of trabecular endothelial cells
- Increase in accumulation of pigment
- Thickening and fusion of the trabecular lamellae
- Thickening of scleral spur
- Increase in plaque material
    - Extra cellular matrix deposited between juxtacanalicular endothelial cells and Schlemm's canal
    - Loss of ability to form giant vacuoles along inner wall of Schlemm's Canal

The glaucomatous changes are as follows:

- Greater loss of trabecular endothelial cells

- Increase in dense plaques
- Enlargement of the endothelial cells and thickening of the lamellar sheets leading to complete obstruction of the uveal and corneoscleral pathways.

INTRAOCULAR PRESSURE (IOP)

A person's IOP is determined to a large degree by the relationship between the inflow and outflow of aqueous humor. An elevated IOP is a strong risk factor for the onset and progression of glaucoma. Historically, an IOP greater than 21 mm Hg separated normal from abnormal.

This definition of glaucoma excluded up to half of people with glaucoma. Today, there is no clear IOP level considered normal or safe as e.g. glaucomatous damage can be observed at 18 mm Hg and another person with IOP of 30 mm Hg may have no damage.

> 21 mm Hg = Ocular Hypertension

DISTRIBUTION OF INTRAOCULAR PRESSURE MEASUREMENTS

The frequency distribution of IOP measurements is shown in Figure 9.4.

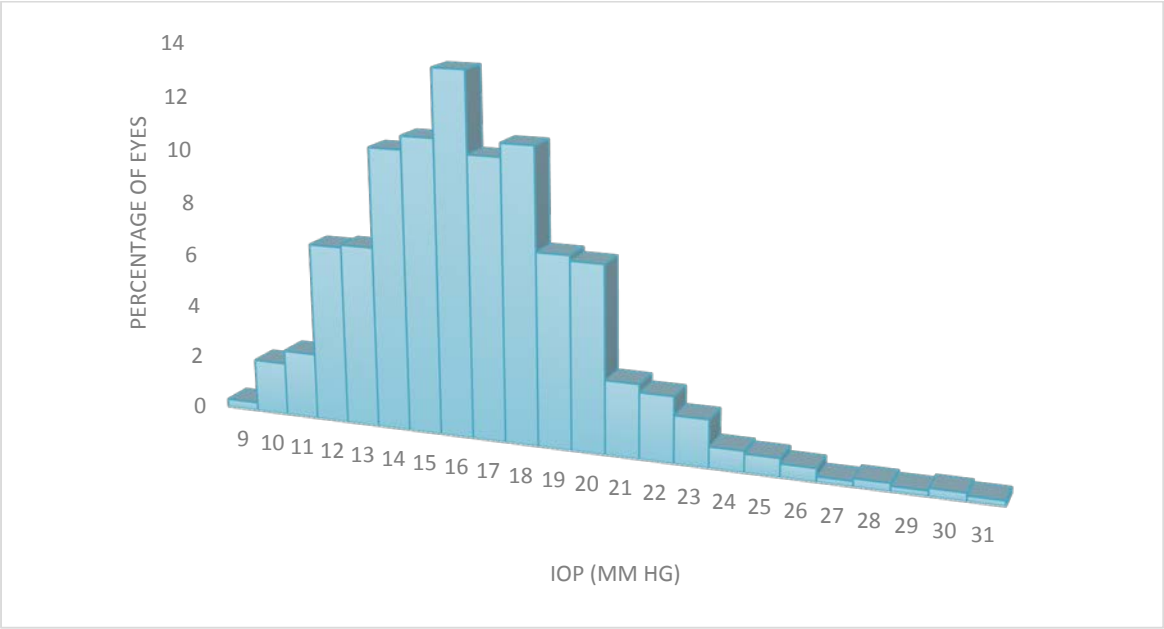


Figure 9.4: *The frequency distribution of IOP*

Adapted from Colton T, Ederer F, The distribution of intraocular pressures in the general population. Surv Ophthalmol, 1980, 25: 123-129.

FACTORS AFFECTING IOP

There are numerous factors that play a role in the level at which the IOP is measured. Some of the major factors are as follows:

- Exercise
  - Strenuous exercise lowers the IOP

- Fluid intake
  - Caffeine and excessive fluid increases the IOP
  - Alcohol decreases the IOP
- Systemic medications
  - Blood pressure medications lowers the IOP
  - Systemic beta-blockers (*atenolol, metoprolol*), calcium channel blockers *(Verapramil, Diltiazem),* carbonic anhydrase inhibitors *(diuretics: hydrochlorothiazide, furosemide, chlorthalidone, etc)*
  - Corticosteroids increases the IOP
  - Topical medications lowers or increases IOP depending on the medication
- Body position
  - Lying down increases the IOP

CHARACTERISTICS OF IOP

One of the main characteristics of IOP is that it displays a diurnal variation. The key features of research on IOP variability indicate the following:

- Peak of the IOP is in early morning when still asleep
- IOP varies 2-6 mm Hg over a 24 hr period
- Higher IOP value results in a greater diurnal fluctuation
- Impact of the diurnal IOP fluctuation on optic nerve damage is still unknown

GLAUCOMATOUS OPTIC NEUROPATHY

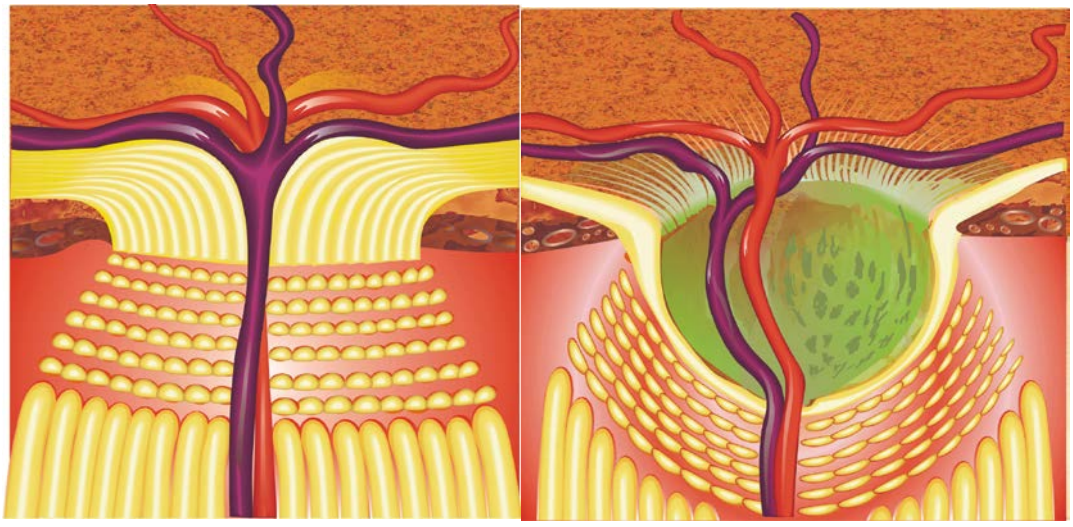


Figure 9.5: *The normal optic nerve head appearance on the left and the cupping associated with glaucoma on the right*

The normal and glaucomatous optic nerve appearances are shown in Figure 9.5.

The anatomy and physiology of the following layers are important considerations when discussing the development of glaucomatous optic neuropathy:

- Retinal ganglion cell
- Retinal nerve fiber layer
- Optic disc
- Intraocular optic nerve

- Prelaminar section
- Lamina cribrosa
- Intraorbital optic nerve
- Retrolaminar optic nerve

THE OPTIC NERVE

The optic nerve can be divided into the intraocular and intraorbital components (Figure 9.6).

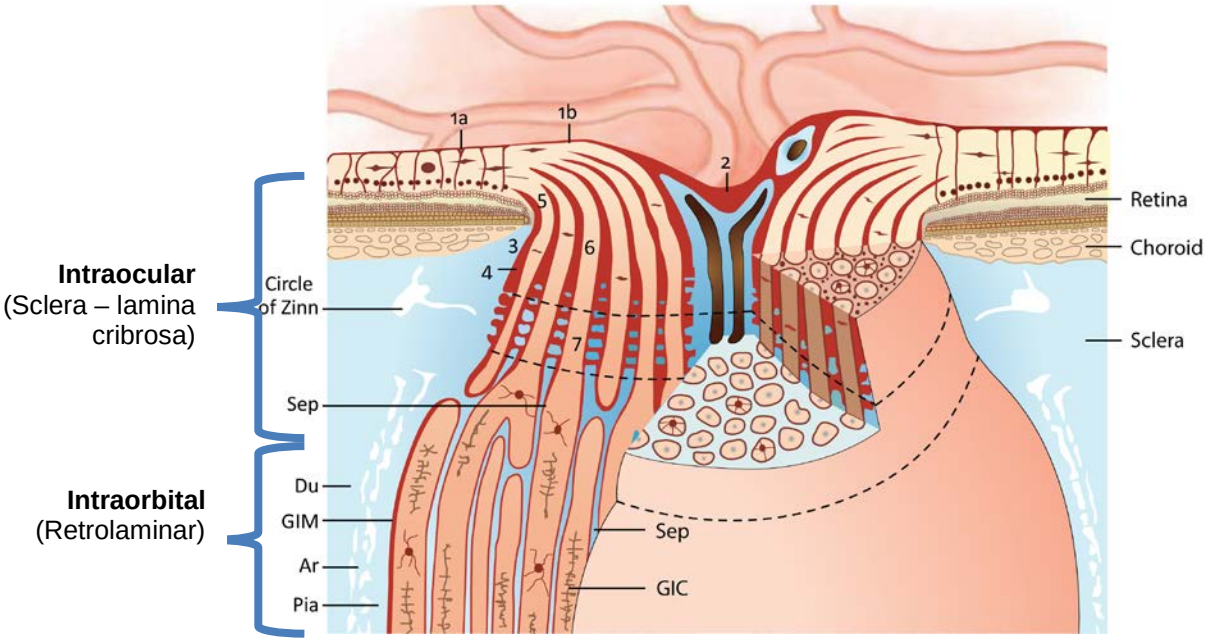


Figure 9.6: *Components of the optic nerve*

INTRAOCULAR PORTION: RGC AND RNFL

The main characteristics of the retinal ganglion cells (RGC) and nerve fiber layer (RNFL) are as follows:

- Last cell layer in the visual pathway in the retina is the ganglion cell layer
  - Also comprised of displaced amacrine cells, Muller cells, and astroglial cells
- Retinal nerve fiber layer arises from the axons of ganglion cells and courses toward the optic nerve in a characteristic pattern
  - Axons near the center of fixation course away from the fovea and then towards the optic nerve (Figure 9.7)
  - Superior/inferior fibers do not cross the horizontal raphe (Figure 9.8)
- There are approximately 1.2 million RGC axons

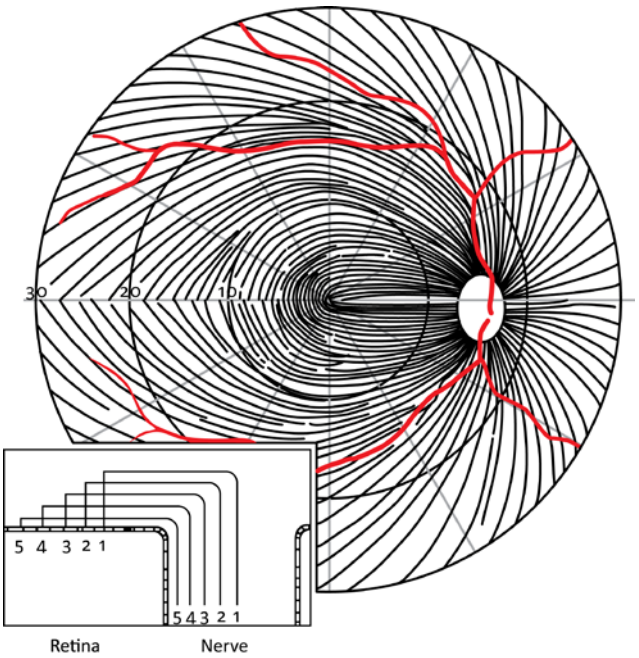


Figure 9.7: *Course of the retinal nerve fibers*

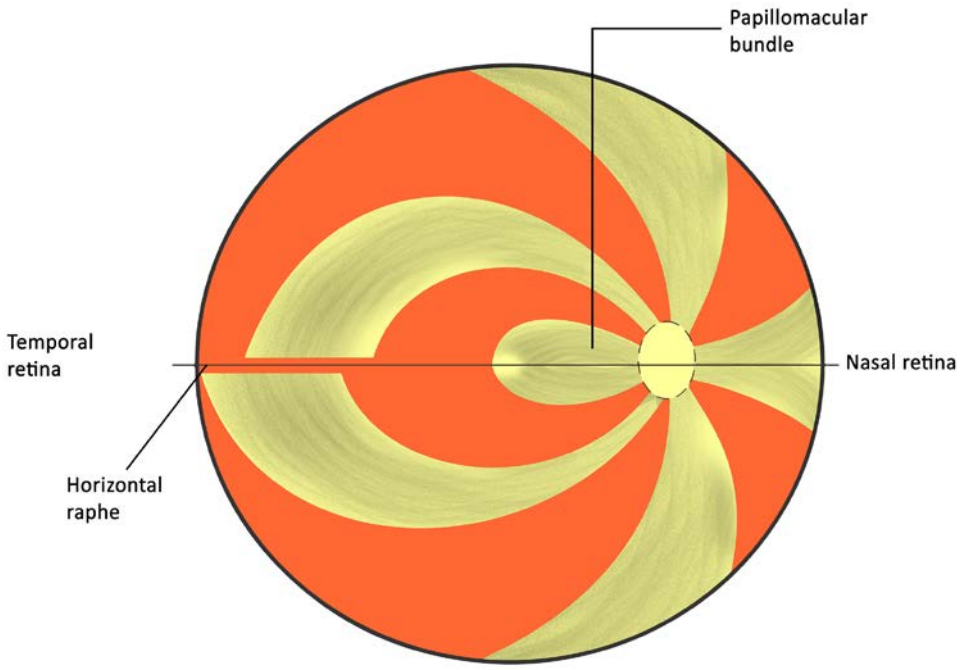


Figure 9.8: *Nerve fibers respect the horizontal raphe*

INTRAOCULAR PORTION: OPTIC DISC

The main characteristics of the optic disc are as follows:

- The thick internal limiting membrane (ILM) of the retina merges with the thinner ILM on the surface of the optic nerve
- Nerve fibers make an approximate 90^0 turn and exit at the optic nerve
- Optic Disc
    - Comprised of neuro-retinal rim and optic cup

        - Neuroretinal rim is comprised of nerve fibers
        - More fibers are concentrated superiorly and inferiorly
    - Optic cup has no retinal nerve fibers
    - Vertically elongated
        - Vertical diameter: approximately 1.9 mm (1.0-3.0 mm)
        - Horizontal diameter: approximately 1.7-1.8 mm (0.9-2.6 mm)
        - Area: approximately 2.7 mm^2
    - Axons follow a distinct retinotopic pattern
        - Nasal fibers radiate to the nasal side of the optic disc, papillomacular bundle courses directly to the temporal side of the optic nerve
        - Fibers from peripheral retina may be more superficial than those coming from central retina

INTRAOCULAR PORTION: PRELAMINAR REGION

The main characteristics of the prelaminar region are as follows:

- Located between the surface of the optic nerve head and the anterior border of the scleral lamina cribrosa
- Contains axons of ganglion cells along with their supporting glial tissue and blood vessels
    - Glial cells make up 50% of the volume of the prelaminar portion of the optic nerve – part of the ILM covering surface of the nerve
        - Prominent glial cell present: fibrous astrocyte
    - Astrocytes surround the axons like tubes
    - Very little connective tissue except for around blood vessels
- Center of the prelaminar region does not contain axons but contains additional fibrous astrocytes

ASTROCYTES

The main features of the role played by astrocytes are as follows:

- The major cell type in the optic nerve
    - Glial cells (along with LC cells)
- Vital to the health of RGCs
- Responsible for the nerve fiber layer striations
- Maintain extracellular environment
- Uptake of K+ and glutamate from extracellular space
- Provide neurotrophic support for adjacent neurons at each section of the nerve
    - Prelaminar: Form glial tubes for axons (90 degrees turn)
    - Laminar: Surround the laminar beams and produce collagens and elastins

INTRAOCULAR PORTION: LAMINA CRIBROSA

The main characteristics of the lamina cribrosa (Figure 9.9) are as follows:

- Extension of sclera across the posterior scleral foramen
- Reinforces the posterior eye by forming scaffolding to support the nerve fiber bundles
    - 10 lamellae (layers) of connective tissue
    - Separated by fibrous astrocytes and fenestrated to allow for passage of nerve fiber bundles and blood vessels
    - Anchored peripherally to sclera, centrally to central retinal vessels and posteriorly to the septa of the retrolaminar optic nerve
    - Allows passage to nerve fiber bundles and blood vessels
    - Combination of elastin and collagen to provide tensile strength and resistance to distortion
- Approximately 200-600 pores within lamella, size varies between10-250 um

Figure 9.9: *Cross-section of the lamina cribrosa*

INTRAORBITAL REGION: RETROLAMINAR

The main characteristics of the retrolaminar region are as follows:

- Extends from posterior surface of the scleral foramen to the lateral geniculate nucleus (LGN)
- Myelin surrounds the axon bundles and there is a decrease in astrocytes
- Meningeal sheaths cover the surface of the optic nerve
- Diameter of the optic nerve doubles
- Path of the optic nerve:
    - Enters the cranium via the optic canal (5-12 mm)
    - From cranium moves to chiasm (12 mm)
    - Optic nerve anatomically ends at chiasm, but RGC axons continue within the optic tract until the lateral geniculate nucleus

AXONAL TRANSPORT

Axonal transport is the process in which neurons move components from the cell body to the axons to survive. A breakdown in axonal transport is responsible for cell death.

The main characteristics of axonal transport in the optic nerve are as follows:

- Cells must be able to transport material within their cytoplasm to all areas of the cell including axons which do not contain organisms usually found in cytoplasm
- Transport of cytoplasmic material via microtubules within the axon from the cell body to the nerve synapse
- Energy dependent process essential for survival of the axon and nerve cell
    - Transports material necessary from cell body to supply the nerve synapse, and transports by-products of metabolism back from the synapse to the nerve cell body for digestion
- Orthograde (anterograde): forward transport
- Retrograde: backward transport
- Blockage of axonal transport results in cell death
    - A reduction in blood supply to the nerve cell or any portion of the axon can lead to ischemia and cell death
    - Mechanical compression of the axons decreases growth factors needed for survival

BLOOD SUPPLY TO THE OPTIC NERVE

Blood supply to the optic nerve is important because of implication of decreased perfusion to the optic nerve in the pathogenesis of glaucoma.

The blood supply to the optic nerve (Figure 9.10) comes from the posterior ciliary arteries and the central retinal artery which branch from the ophthalmic artery.

Usually two to three posterior ciliary arteries are distributed on the medial and lateral side of the optic nerve (Figure 9.11) where these arteries form both long (LPCA) and short (SPCA) branches. Each posterior ciliary artery is an end-artery system – they supply a specific territory of tissue with no anastomoses between vessels and thus a watershed area is created at the outer edges of the territory supplied by adjacent posterior ciliary arteries.

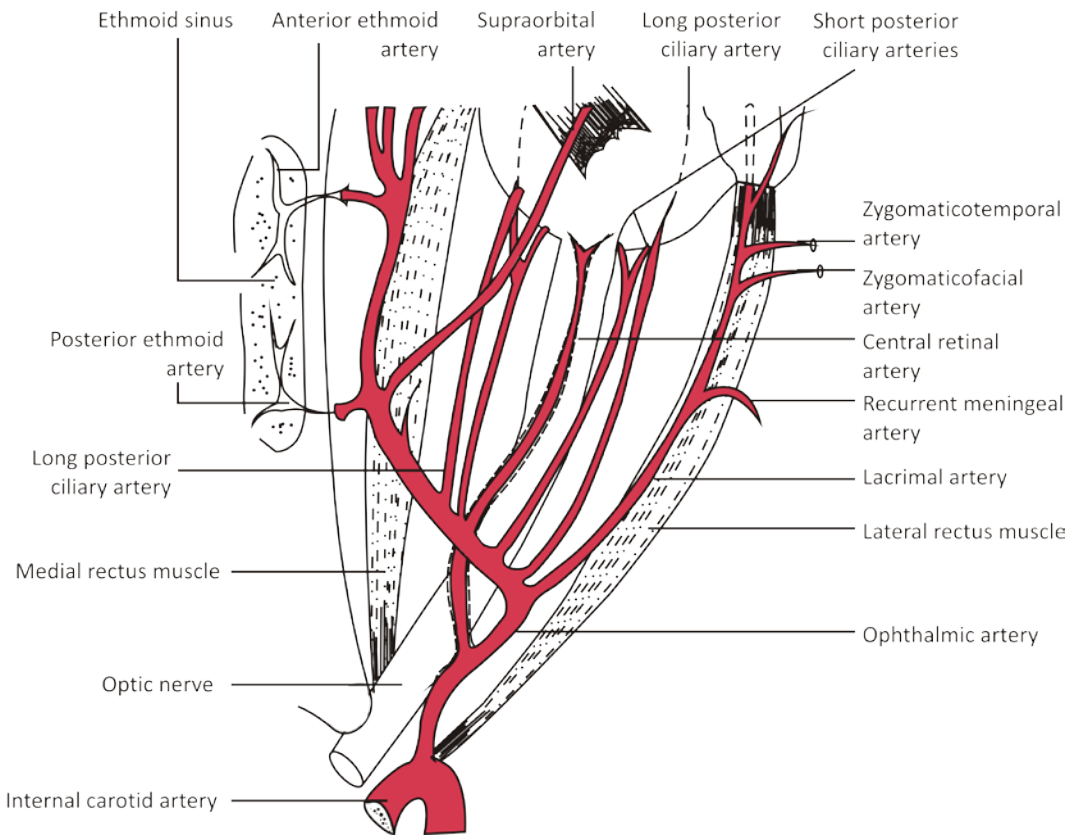


Figure 9.10: *Vascular supply to the eye*

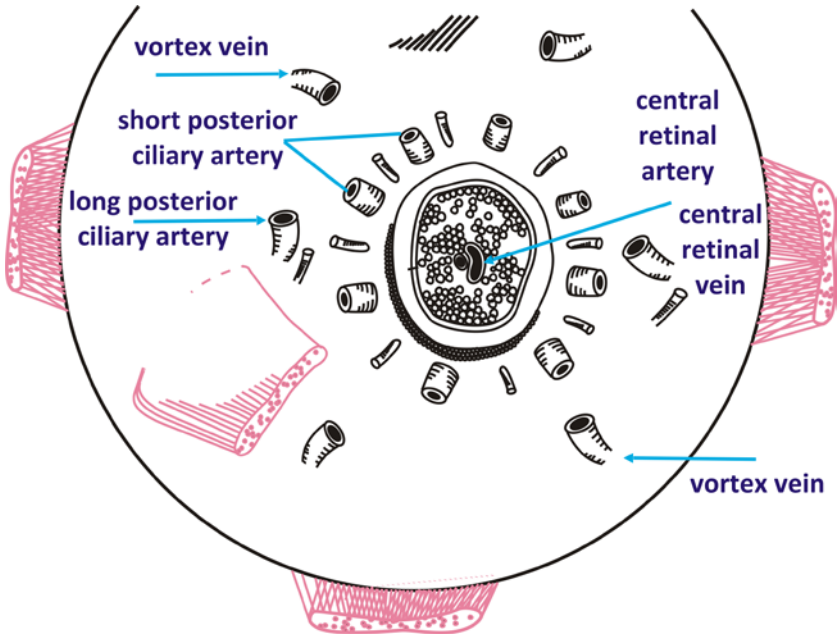


Figure 9.11: *Blood supply seen from behind the eyeball*

If blood flow of a particular artery is obstructed, there will be no way of getting blood and oxygen to that tissue section and ischemia will ensue.

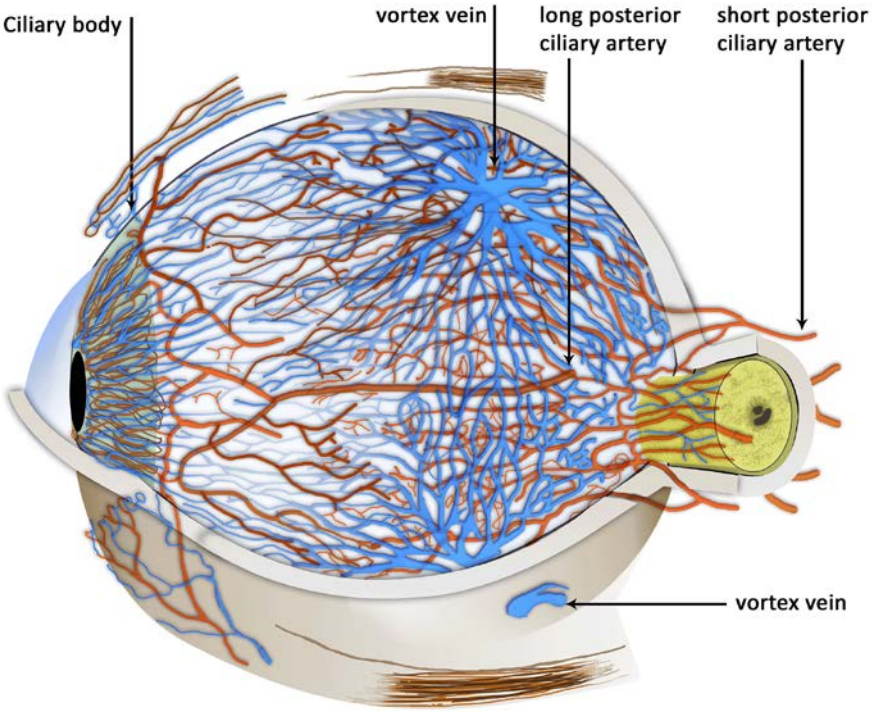


Figure 9.12: *Vascular supply to the eye*

NERVE FIBER LAYER BLOOD SUPPLY

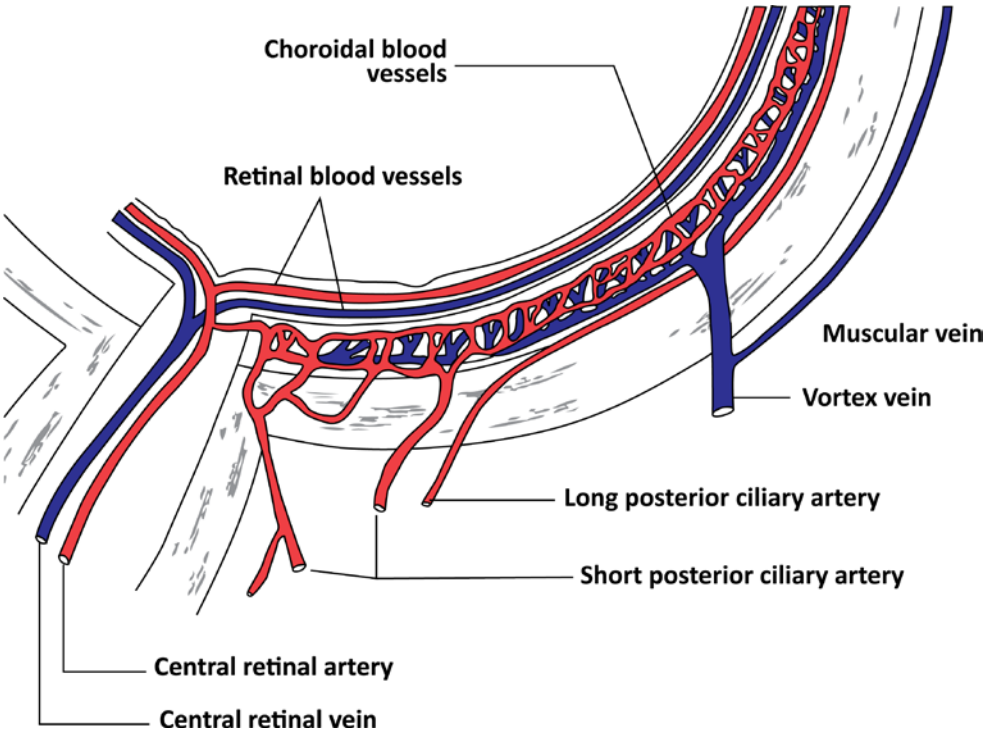
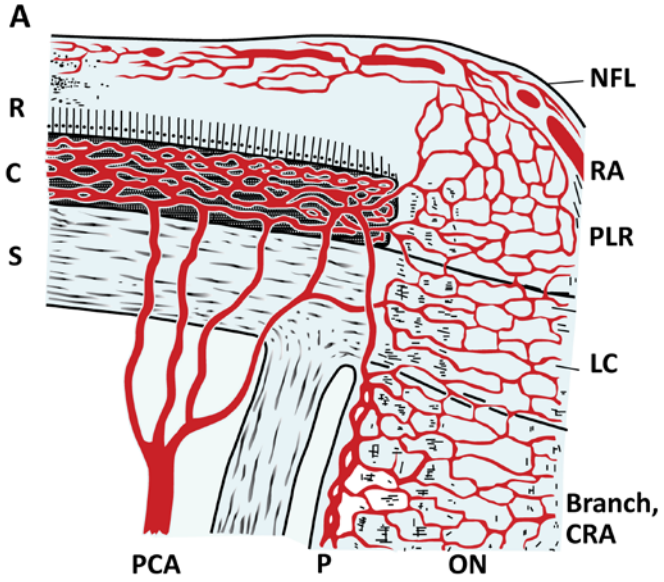


Figure 9.13: *Vascular supply to the nerve fiber layer*

The nerve fiber layer is supplied by branches of the central retinal artery with venous drainage into the central retinal vein (Figure 9.13).

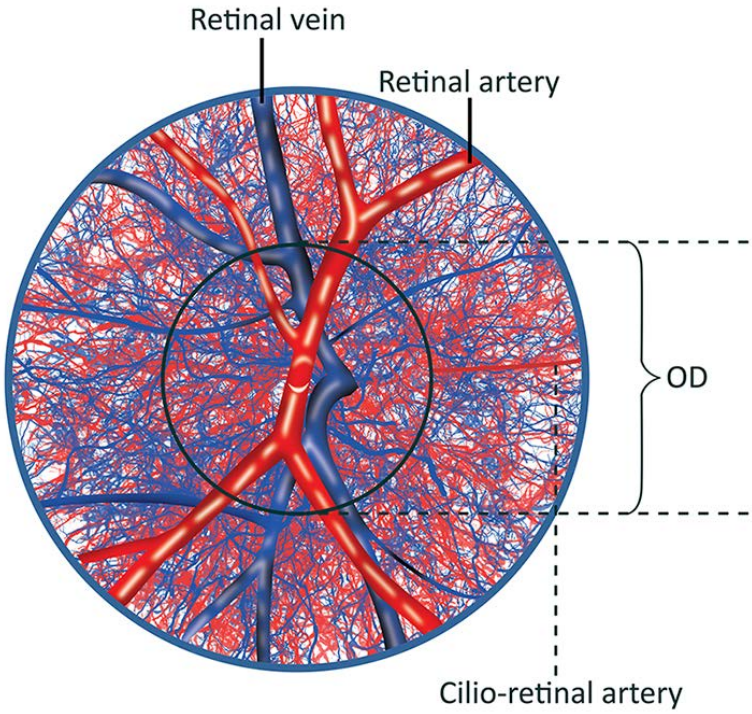
There is a continuous capillary network from the level of the surface nerve fibers back through the post-laminar region of the optic nerve. Capillaries on the surface of the optic nerve are also continuous with those in the peripapillary retina.

A schematic representation of blood supply to the optic nerve head and the optic nerve is shown in Figures 9.14 and 9.15 respectively.



A = arachnoid
C = choroid
CRA = central retinal artery
Col. Br. = collateral branches
CRV = central retinal vein
D = dura
LC = lamina cribrosa
NFL = surface nerve fiber layer of the disc
OD = optic disc
ON = optic nerve
P = pia
PCA = posterior ciliary artery
PR and PLR = prelaminar region
R = retina
RA = retinal arteriole
S = sclera
SAS = subarachnoid space

Figure 9.14: *Vascular supply to the optic nerve and nerve fiber layer (Hayreh 1978)*



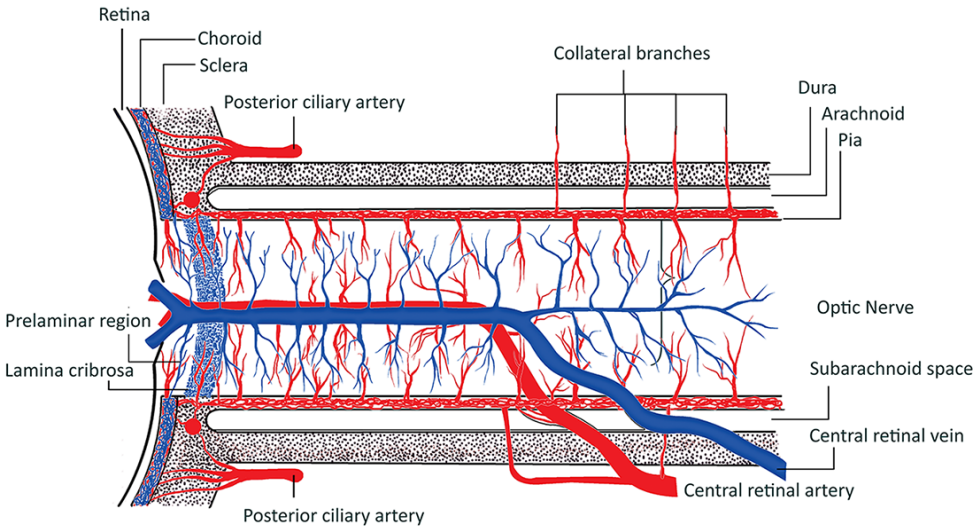


Figure 9.15: *Vascular supply to the optic nerve (Hayreh, S.S. 1974)*

The prelaminar region receives blood supply from branches of the peripapillary choroid. These branches arise from short posterior ciliary arteries and have a segmental/sectoral distribution.

- No anastomoses exist between vessels supplying the optic nerve and the choriocapillaris at this level – longitudinal capillary networks connect the tissues of the laminar, prelaminar and nerve fiber layers.
- The central retinal artery and its branches play no role in the blood supply to this area -
- Temporal portion of the prelaminar region may be more vascularized than other areas
- Capillaries from the prelaminar region drain into central retinal vein or through the choroid into the vortex veins

The laminar region contains a centripetal system located within the lamellae and a longitudinal system of capillaries interconnecting with various regions within the optic nerve (Figure 9.17)

- Major centripetal supply is from circle of Zinn-Haller – formed by anastomosis within the sclera to just outside the optic nerve from branches of adjacent SPCA
- CRA plays little role
- Venous drainage is via the CRV

In the intraorbital region the blood supply is more complex than in other portions – consists of one network of vessels supplying the periphery and another supplying the central portion.

- Peripheral portion is supplied by branches from the pia matter's vascular plexus. This plexus is formed by branches from muscular arteries, the ophthalmic artery, and recurrent branches.
  - In addition, help from the peripapillary choroid and the circle of Zinn-Haller
- The central retinal artery contributes small branches to the central or axial portion of the postlaminar region of the optic nerve
- Venous drainage in through the CRV

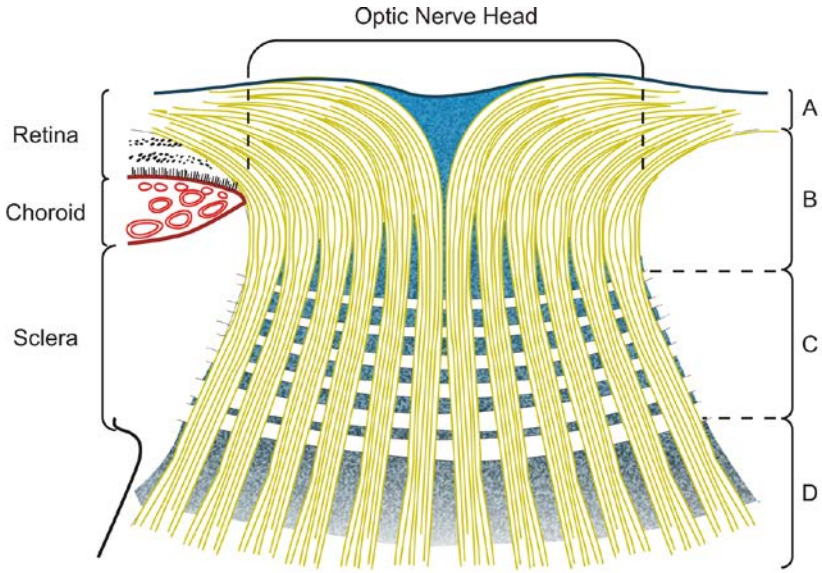


Figure 9.16: *Division of the optic nerve*

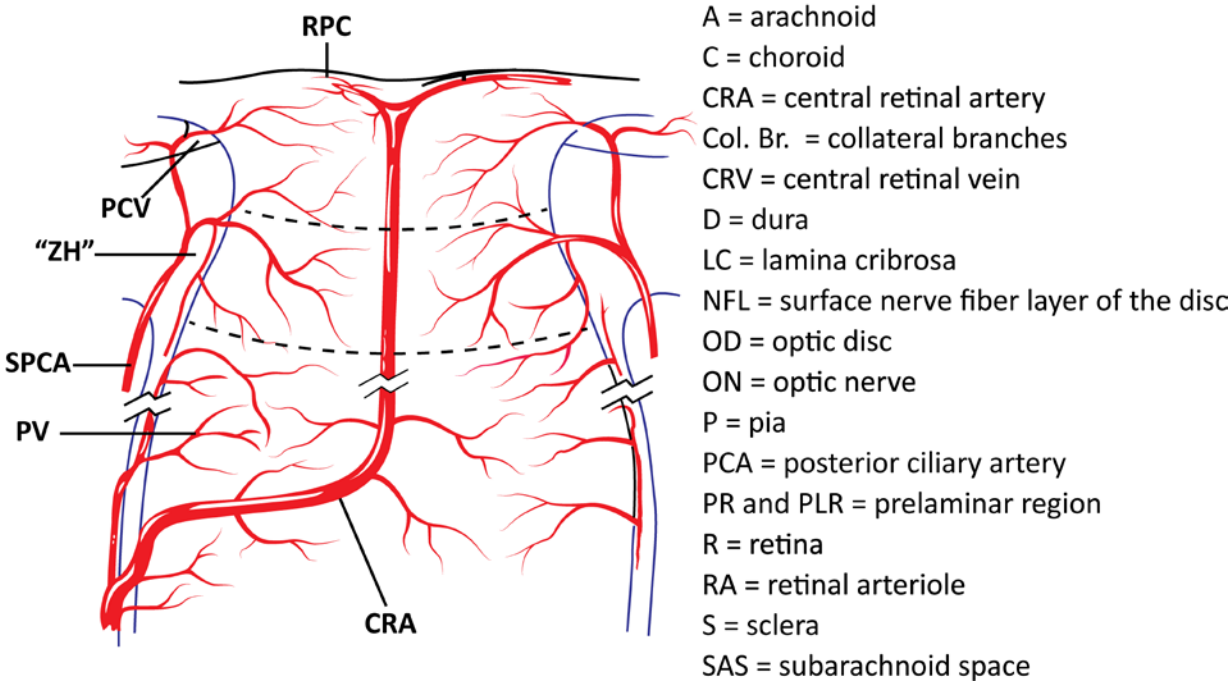


Figure 9.17: *Vascular supply to the optic nerve head*

CRA*:* central retinal artery
RPC*:* radial peripapillary capillaries
PV*:* pial vessels
SPCA: short posterior ciliary arteries;
PCV*:* peripapillary choroidal vessels;
ZH*:* "circle" of Zinn-Haller

BLOOD VESSELS OF THE OPTIC NERVE

The main features of the blood vessels in the optic nerve are as follows:

- Blood vessels in the optic nerve have non-fenestrated endothelial cells
- Optic nerve vessels auto-regulate
- Have the ability to maintain constant blood flow at all times despite changes in intraocular pressure
- Thus, in a normal healthy eye, there is no change to perfusion in the optic nerve despite daily fluctuations in blood pressure and IOP
- In disease states, the autoregulation will break down leading to a decrease in perfusion of blood flow to the optic nerve and resultant optic nerve damage

PERFUSION PRESSURE

The main characteristics of perfusion pressure are as follows:

- The pressure that circulates blood inside vessels
    - When low, little blood flow gets to target tissue
- In the eye, it is equal to the difference between the mean arterial blood pressure and intraocular pressure

Mean ocular perfusion pressure (MOPP) = ⅔ (mean arterial pressure − IOP),

[mean arterial pressure (MAP) = DBP + ⅓ (SBP − DBP)]

Mean ocular perfusion pressure can be simplified to MOPP = DBP - IOP

Low DBP, low MOPP, and low DPP are independent risk factors for OAG.

DBP = diastolic blood pressure
SBP = systolic blood pressure
IOP = intraocular pressure

OCULAR PERFUSION PRESSURE

A diagram representing the ocular perfusion pressure is shown in Figure 9.18.

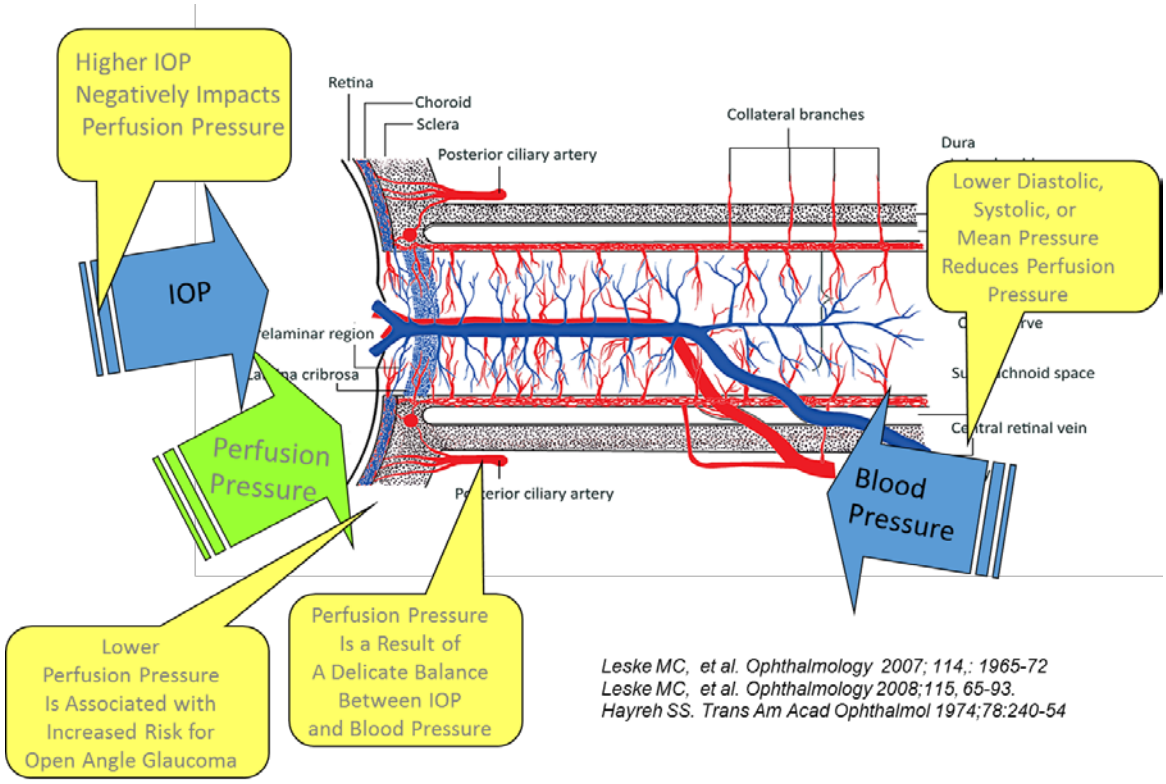


Figure 9.18: *Perfusion pressure at the optic nerve*

HABITUAL IOP AND PULSE PRESSURE

The diastolic blood pressure dips down low at night which acts against IOP rising in the morning (Figure 9.19).

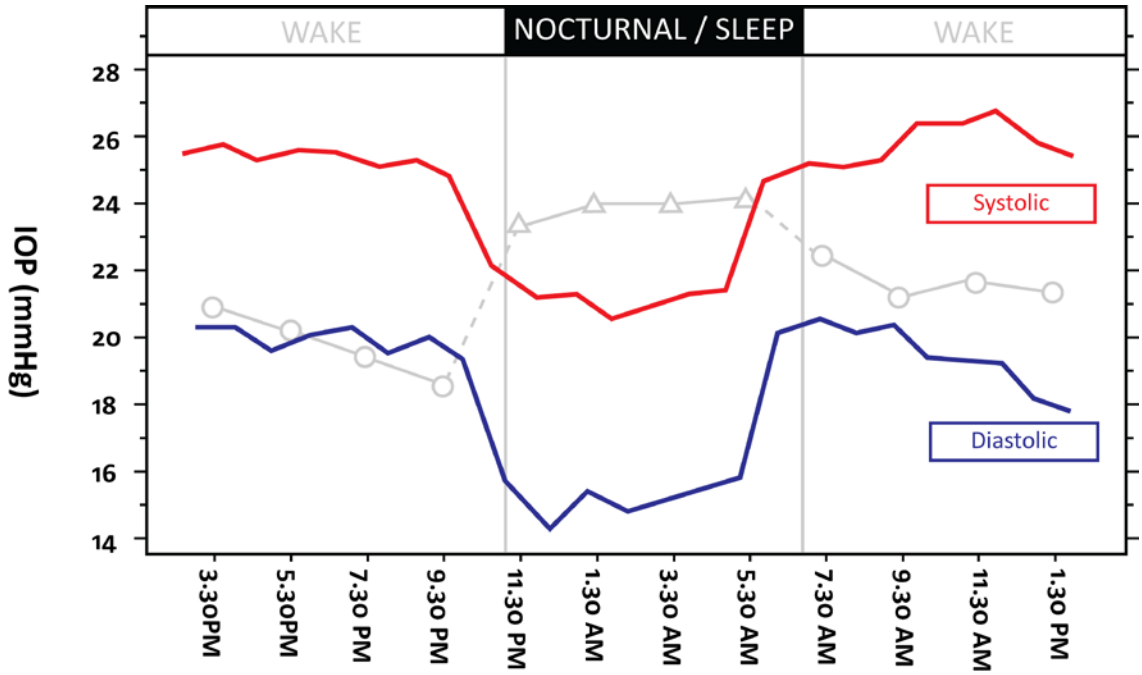


Figure 9.19: *Diurnal variation in blood pressure*

SUMMARY OF ANATOMY AND PHYSIOLOGY PERTINENT TO GLAUCOMA

- Optic nerve is anatomically divided into intraocular and intraorbital sections
- The optic nerve is comprised mainly of nerve fiber axon bundles surrounded by astrocytes for support
- The axons pass through the pores of the lamina cribrosa and transport nutrients via axonal transport
- Disorganization/compression of the pores in the lamina cribrosa may disrupt axonal transport
- Blood supply in the optic nerve is dependent on anatomical portion:
    - RNFL: Central Retinal Arterioles
    - Prelaminar: SPCA
    - Lamina cribrosa: SPCA and to a lesser extent the CRA
    - Post-lamina: Pia vasculature and the CRA

DEVELOPMENT OF GLAUCOMA AND THE GLAUCOMA CONTINUUM

The development of glaucoma from the normal state through to blindness is shown in Figure 9.20.

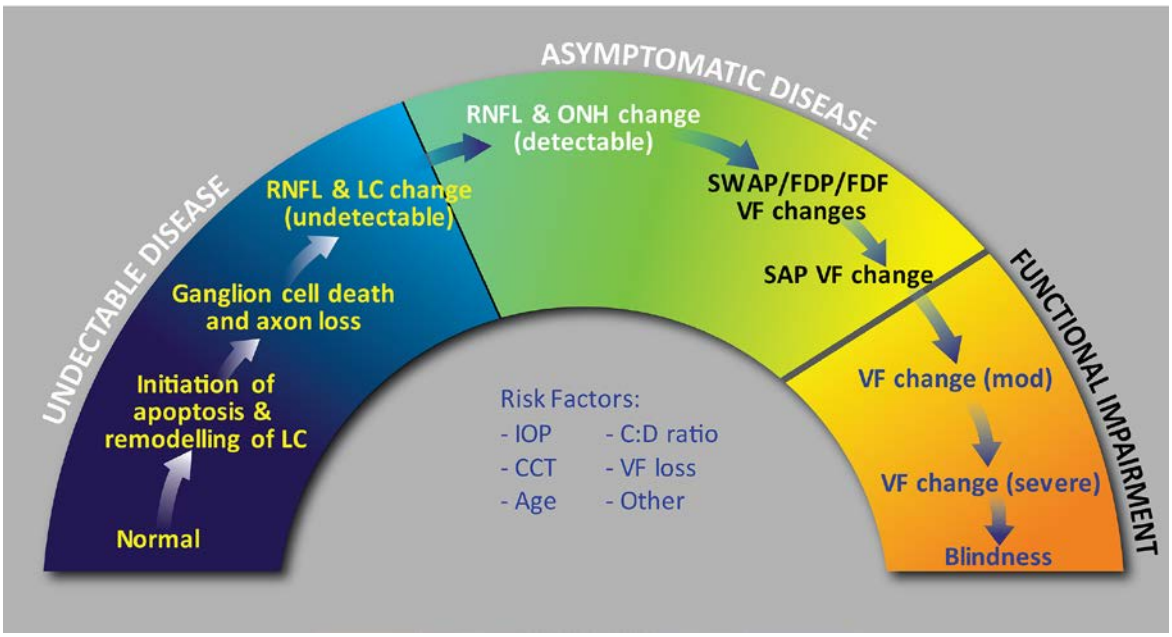


Figure 9.20: *The glaucoma continuum*

WHY DOES GLAUCOMATOUS OPTIC NEUROPATHY DEVELOP?

The main stressors on the eye and their potential effects are shown below.

Stressors		Effects
Metabolic Dysfunction	→	Glial Activation
Immune Compromise		Cytokine Production
Oxidative Stress		Stress Response Enzymes
Genetic		RGC Death by Apoptosis
Biomechanical		ECM Remodeling
Ischemic		

HOW DOES OPTIC NEUROPATHY DEVELOP?

The impact of elevated IOP and the associated pathophysiology of glaucoma are shown in Figure 9.21.

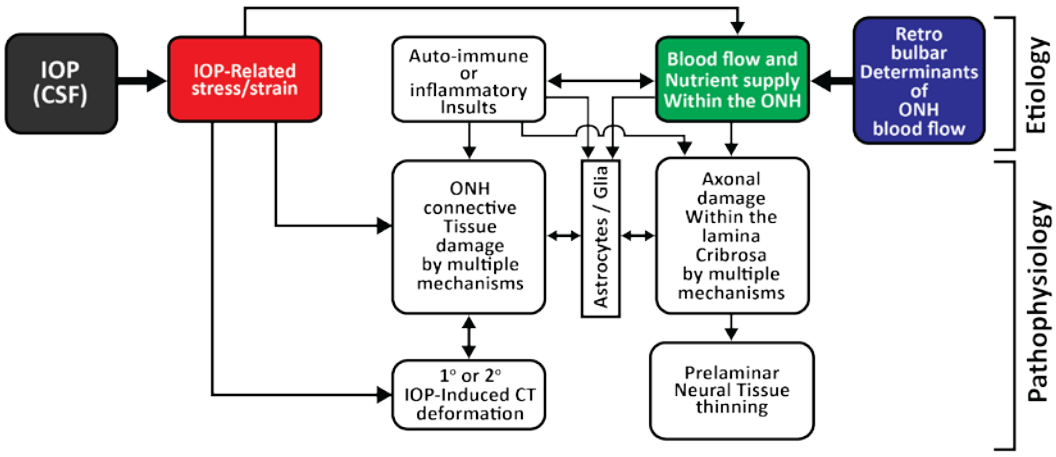


Figure 9.21: *The development of optic neuropathy*

Initial insult leads to the following:

1. Remodeling of the lamina cribrosa
2. Axonal damage
    - Loss of retinal ganglion cells
    - Impact on Structure/Function relationship
3. Loss of neuroretinal rim

REMODELING OF THE LAMINA CRIBROSA

The main characteristics of the lamina cribrosa in glaucoma are as follows:

1. Compression, stretching and remodeling of the sheets of the scleral lamina cribrosa
2. Posterior displacement of the laminar sheets
3. Distortion and/or enlargement of the laminar pores
4. Transformation of type 1β astrocytes
5. Extensive remodeling of the laminar sheets and extracellular matrix
6. Loss of compliance or increase in stiffness of the scleral laminar cribrosa
7. Absence of inflammation or scarring

ASTROCYTE-MEDIATED CHANGES

- Usually first to react to injury, therefore likely a key player in pathogenesis of glaucoma regardless of cause
- Dysfunction predisposes to:
    - Disruption of axoplasmic transport
    - Changes in cribrosal physiology
        - Death of retinal ganglion cells

- Transformation of type 1β astrocytes from quiescent to reactive state
  - Increase in Type VI collagen
  - Reactivation of elastin synthesis
  - Proliferation of basement membrane and increase in Type IV collagen
  - Increase in synthesis of TGFβ2, an important cytokine
    - modulator in wound healing
    - inducer of reactive astrocytes
  - Increase in synthesis of tenascin

COMPRESSION OF THE AXONS THROUGH LAMINA CRIBROSA

Blockage of axoplasmic (axonal) transport and ganglion cell death

BLOCKAGE OF AXOPLASMIC FLOW

- Blocks both orthograde (GC to LGB) transport and retrograde transport (LGB to GC)
- Causes destruction of ganglion cell (GC)

GANGLION CELL DEATH INDUCED BY APOPTOTIC CASCADE

Apoptosis

- Biological process
- Programmed cell death
  - Loss of neurotrophic support
    - due to blockage of retrograde transport
  - Overexposure to glutamate
    - occurs in ischemic/hypoxic conditions
- No necrosis, no inflammation
- Insult to a neuron cell body will result in factors to be released that cause apoptosis in nearby neurons

THEORIES OF GLAUCOMA DEVELOPMENT

MECHANICAL THEORY

The main features of the mechanical theory are as follows:

- High IOP causes direct damage to the optic nerve and ganglion cells causing structural changes
- Creates a pressure gradient that compresses the laminar sheets and bows them outward
  - Distortion of pores
  - Pinches ganglion cells axons as they pass through this area
- Difficult to explain normal tension glaucoma with this mechanism

VASCULAR THEORY

The main features of the vascular theory are as follows:

- Decrease in blood flow to the lamina cribrosa causes blockage of axoplasmic flow
  - Due to a reduction in energy available lowering metabolic activity
  - Evidence supports localized blockage of rapid axonal transport with decrease in blood flow
- Abnormal auto-regulation resulting in ischemia
- PPA may be an indicator of poor choroidal circulation
- Best mechanism to explain normal tension glaucoma (NTG)

TRANSLAMINAR CRIBROSA PRESSURE THEORY

The main characteristics of the translaminar cribrosa pressure gradient are as follows:

- Pressure gradient exists between intraocular and retro bulbar CSF and is dependent on thickness of the lamina cribrosa (Figure 9.23)
    - Normal is a difference of about 4 mm Hg (CSF is normally lower than IOP)
    - Abnormal pressure gradient influences physiology of optic nerve fibers and axonal transport
    - May cause changes to organization of the pores within lamina cribrosa

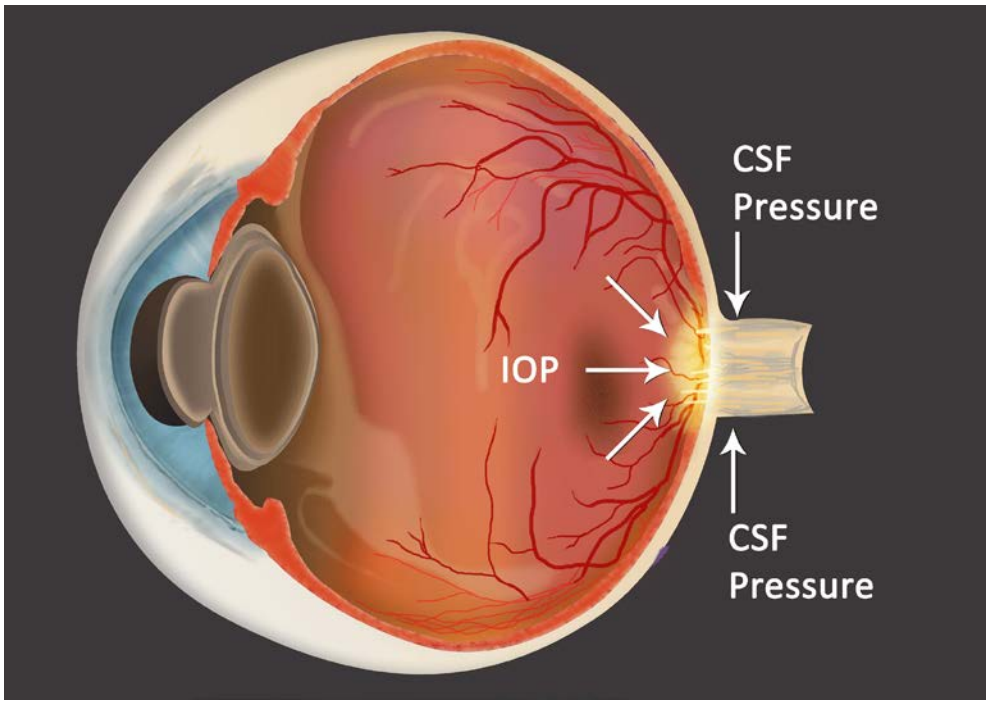


Figure 9.22: *IOP and retro bulbar cerebrospinal fluid pressure*

High IOP or Low CSF will create an abnormal Translaminar Cribrosa Pressure (Figure 9.24).

A higher difference is correlated to loss of neuroretinal rim area.

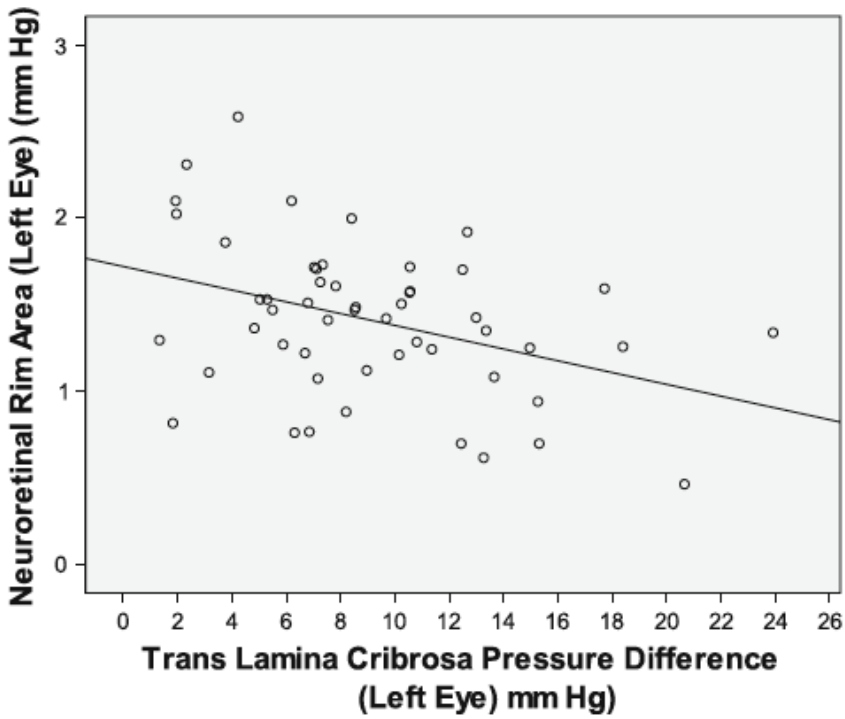


Figure 9.23: *Relationship between translaminar cribrosa pressure difference and neuro-retinal rim area*

Translaminar Cribrosa Pressure Difference = IOP – CSF_{lumbar}

FOUR COMPARTMENT MODEL OF OPTIC DISC PRESSURE RELATIONSHIPS

Retrolaminar optic nerve is affected by optic nerve subarachnoid space (ONSAS) which is connected to intracranial CSF space – ONSAS is surrounded by orbit which may set a minimum optic nerve subarachnoid space pressure (Figure 9.22)

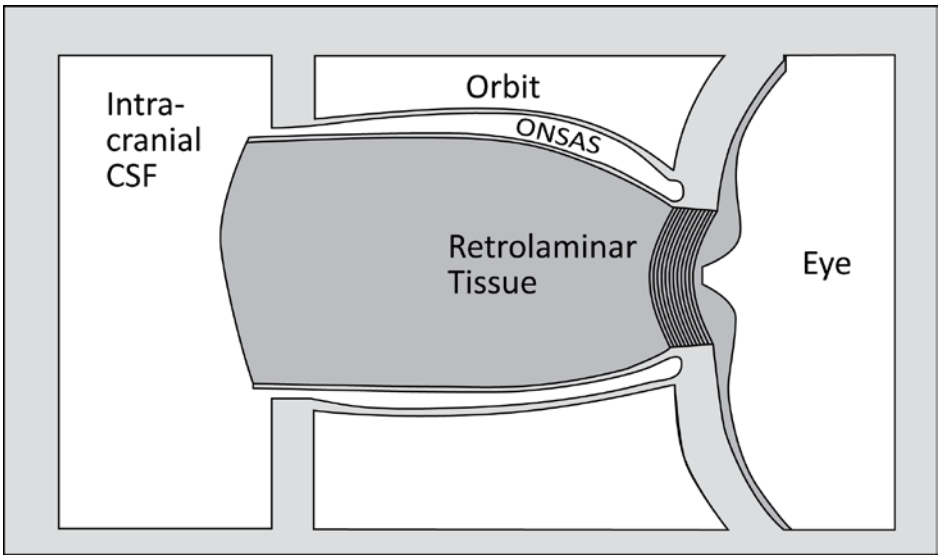


Figure 9.24: *The four compartment model of optic disc pressure*