Ocular Perfusion and Glaucoma
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It’s Not Complicated…or is it?

It is well known that IOP reduction is beneficial in open-angle glaucoma (OAG) regardless of the baseline IOP.

1. WHY does lowering the IOP help reduce progression?
2. WHY do some patients progress despite a low target IOP?

But what causes this?
But what causes This?

What in the Normal Physiology of the ONH is Affected that Causes Glaucomatous Optic Atrophy?

Axonal Transport

• Ganglion cell axons run from retina through nerve, orbit and Chiasm to Lateral Geniculate Body.
  • Nutrients must be delivered along the entire axon.
• Axonal transport is
  • energy dependent
  • Oxygen dependent
  • glucose dependent from normal blood flow.

• Interruption of blood flow to the axons (injury, ischemia, hypoxia) will reduce axonal transport.
• Axonal death may develop in days/weeks or months/years from compromised blood flow.

Loss of axons ultimately leads to “excavation” and “cupping” of the optic nerve head

How does interruption of axonal transport cause cupping in glc?

• 2 primary theories on the origin of glaucomatous cupping
  • Mechanical Theory
  • Vascular Theory

Normal ONH Anatomy

RNFL is composed of the RGC, Muller’s cells

The axons of the retinal ganglion cell (RGC) exit the eye through the lamina cribrosa.

- RGC axons become myelinated post-laminar region.
- With normal axonal transport, RGC are functioning and quiet.

Increased IOP puts “stress” on RGC causing a reaction to the stress.

- Elevated IOP leads to the production of a variety of substances which damage the RGC axon at the lamina cribrosa.

Damage to the RGC axon is followed by cell death through apoptosis.

- Loss of the axons followed by RGC loss results in thinning of the RNFL.
- The lamina cribrosa initially becomes thicker and bows posteriorly.

This results kinking of the laminar pores and further reduces axonal transport.

- This leads to apoptosis, cell death, and loss of the RGC and axons.
- This causes increased cupping of the ONH.
- The prelaminar tissue becomes attenuated and the lamina cribrosa now becomes thinner and bowed more posteriorly contributing to more cupping.

Summary of Mechanical Theory

- Misalignment of the lamina cribosa or movement and displacement of ganglion cell axon bundles.
- Backward bowing of the LC causes cupping.
- This “kinking” results in blockage of axonal transport.
- Ultimately axonal death occurs and more cupping.
- Well accepted at high IOP’s GLC.

Lamina Deformation

- The mechanical theory shows that the lamina cribrosa deformation contributes to the loss of axonal transport which damages the ganglion cells in the ONH.
• Posterior deformation of the LC depends not only on the IOP, but also on the geometry and material properties (i.e., thickness, compliance, or rigidity) of the ONH and the peripapillary scleral tissue.

Burgoyne CF. A biomechanical paradigm for axonal insult within the optic nerve head in aging and glaucoma. Exp Eye Res 2011;93:120–32.

Principle distribution of forces, pressures and the translaminar pressure gradient within the optic nerve head

RLTP = retrolaminar tissue pressure

Early GLC is “laminar” in origin
Trans-Laminar Cribrosa Pressure Difference Correlated with Neuroretinal Rim Area in Glaucoma

- Translaminar pressure = IOP- CSF

Results:
- Pt with OHTN had higher trans-lamina pressure difference; no VF loss
- Pts with GLC had lower trans-lamina pressure difference
  - Both high IOP and normal tension GLC

**CSF pressure may play role in pathogenesis of Glaucomatous optic neuropathy**

Is CFS important?

- Trans-lamina cribrosa pressure difference was the main pressure parameter associated with the amount of glaucomatous optic nerve damage.
- This shows the importance the counter pressure the CSF exerts against the IOP across the lamina cribrosa of the optic nerve and contribute to the pathogenesis of glaucomatous optic neuropathy.
- Through the CSF pressure, glaucoma is not only an ocular disorder but a cerebral disease.

Can the lamina cribrosa deformation be reversed?

Mechanical Theory...

- Our knowledge of the underlying mechanism for the development of glaucomatous optic neuropathy continues to develop

What about the vascular theory developments?

Review of ONH Blood Flow
Historical: Vascular Theory

- Ischemia (decreased blood flow) lowers axonal transport rate.
  - Reduced/Initiated by mechanical constriction (2nd to high IOP) and/or reduced blood flow (perfusion pressure).
- Ultimately axonal death occurs.
- Explains glaucoma in patients with low or normal IOP's (e.g. NTG)

Ocular Perfusion Pressure and Glaucoma

Why is Ocular Perfusion Pressure a Risk for Glaucoma?

What is Ocular Perfusion Pressure (OPP)?

- OPP is the difference between arterial and venous pressure.
- In the eye, venous pressure nearly equals IOP.
- OPP can be estimated as the difference between arterial BP and IOP.

Low OPP is a Risk for Glaucoma and Progression

- Barbados Eye Study
  - Low systolic BP doubles the risk for glaucoma.
  - Subjects with lowest 20% of diastolic perfusion pressure (DPP) were 3.3 times more likely to develop GLC.
- Proyecto VER Study
  - Pts with DPP of 45mmHg had 3x greater risk of GLC compared to pts with DPP of 65mmHg.
- Egna-Neumarkt Study
  - Pts with DPP > 50mmHg had 4.5 times greater risk that pts with DPP of 65mmHg.
Ocular Perfusion Pressure and Glaucoma

- SPP = SBP – IOP
- DPP = DBP – IOP
  – (perhaps best to use to clinically measure PP)
- MPP = 2/3 mean arterial pressure – IOP
  – Arterial Pressure = DBP + 1/3(SBP – DBP)

Primary and Secondary Insults in Glaucoma and Low OPP

Clinical Example
- 56 yo AA/M
- Current IOP is 25 mmHg OU
- Current BP is 110/70
- OPP is what?
  - 70-25 = 45
- How can we increase OPP?
  - Increase DBP
  - Decrease IOP
- If lower IOP to 15, what is OPP if IOP remains 110/70?
  - 70-15 = 55

Abnormal Autoregulation

Neurovascular Coupling

Low OPP

- May be due to:
  - High IOP
  - Low BP
  - Physiological
  - Over treatment of systemic HTN
  - Nocturnal Hypotension
Clinical Control of OPP

- Lower IOP improves OPP
- Remains number 1 goal!!
- Measure blood pressure on your patients
- Higher systemic BP improves OPP, but you do not necessarily want to raise BP:
  - Stroke #3 cause of death in US behind CVD & CA!
  - Avoid drugs that lower systemic BP beyond patient’s desired systemic control.
  - Avoid nocturnal hypotension.
  - Communicate with PCP

Summary: OPP and Glaucoma

- Low ocular perfusion pressure (OPP) is an important risk factor for glaucoma and for progression
- OPP is amenable to modification by lowering IOP and improving perfusion pressure
- New strategies are needed to take advantage of this modifiable risk factor


Reduced Blood Flow to ONH

1. Is it possible to increase blood flow to the ONH?
2. Are there other factors that are affecting blood flow?

Retrobulbar Blood Flow

Mechanism of Glaucoma has gotten complicated:

Multifactorial!!
Summary of Mechanisms Involved in Glaucoma

- Glaucomatous optic neuropathy can occur in the presence or absence of detectable increased IOP.
- There is no unifying theory, but a large body of conflicting evidence.
- The Mechanical and Vascular theories are intertwined and one affects the other
- POAG is induced by several factors alone or in combination.

  **MULTIFACTORIAL**

Summary of Mechanisms Involved in Glaucoma

- Also several pathological processes can result in the same clinical manifestations (glaucomatous excavation and neuropathy).
- The lamina cribrosa (LC) is important with mechanical damage mechanisms.
- Distortion and compression of the LC causes compression of ganglion cell axons which decrease axonal transport.

Summary of Mechanisms Involved in Glaucoma

- Regional differences in the size of fenestrations in the LC account for distinct, focal damage patterns.
- The optic nerve head microcirculation is also very important in the pathogenesis of glaucoma.
- The collagenous LC is a conduit for the microvasculature.
- In association with high IOP, the microvasculature can be mechanically affected by distortion of the LC, causing decreased blood flow.
- Poor auto regulation in certain individuals may also result in poor blood flow