IOP Dependent and Independent Mechanisms in Glaucoma

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Overview

- Non-IOP Risk Factors
  - Genetics, Diabetes, Lifestyle Factors
- Ocular Perfusion Pressure
  - disclaimer: partially IOP related
- Obstructive Sleep Apnea
- Cerebrospinal Fluid Pressure
  - The next “BIG” thing
- Nutrition, exercise and lifestyle in glaucoma: a literature review

Objectives

1. Understand the basis of high IOP mechanisms in glaucomatous optic neuropathy
2. Understand the relationship between blood pressure and IOP as defined by ocular perfusion pressure
3. Understand the relationship between cerebrospinal fluid pressure and optic neuropathy
4. Understand non-pharmacological measures in contemporary glaucoma management

CASE MZ

72 years old
High Cholesterol
IOP range 17-20mmHg OD, OS
+ Family History
CCT = 550 microns OD, OS

What other History might be important?

- Family History
- Ocular History
  - Topical steroid use
- Medical History
  - Diabetes
  - Systemic Hypertension

Disclosures

- Michael Chaglasian has the following disclosures:
  - 1. Advisory Boards:
    - Allergan, Inc., Alcon Labs, Carl Zeiss Meditec
- Kimberly Reed has the following disclosures:
  - 1. Advisory Board: Alcon, Bausch & Lomb, MedOp
  - 2. Speakers Bureau: Alcon
- The content of this presentation is in no manner influenced by any of the aforementioned parties or companies
Are We Just Measuring IOP Incorrectly or is it More Than That?

**IOP**

IOP Is the Most Prominent and Consistent Glaucoma Risk Factor

- **Ocular Hypertension Treatment Study (OHTS)**
  - CCT of less than 555 μ has higher risk
  - IOP: every 1mmHg higher (>22) increased risk by 10%

- **Early Manifest Glaucoma Trial (EMGT)**
  - Every 1mmHg of IOP reduction lowers risk of progression by 10%

- **Advanced Glaucoma Intervention Study (AGIS)**
  - IOP always under 18mmHg or a mean of 12mmHg has a lower risk of progression

- **Collaborative Normal-Tension Glaucoma Study**
  - 30% reduction of IOP reduces risk of progression
Mechanism Of IOP and Axonal Damage

Mechanism Of IOP Damage

Progression of Excavation

Factors Affecting IOP

- Exercise can provide a transient 20% decrease.
- Alcohol and marijuana lower IOP – though very transiently and unpredictably.
- Steroids (topical/oral) increase IOP.
- Caffeine has NO effect.
- External pressure on eye (lids, fingers)
- Elevated body temperature, raises IOP.
- Numerous hormonal influences.

90% of patients with elevated IOP DO NOT develop glaucoma

30-50% of patients with glaucoma DO NOT have IOP over 21 mmHg
Glaucoma: Non-IOP Mechanisms

Factors Affecting IOP

- Lying down raises IOP (2-4 mmHg), by increasing episcleral venous pressure and causing a decrease in aqueous outflow.
  - Supine position, Postural / Positional effect

Intraocular Pressure Changes and Ocular Biometry During Sirsasana (Headstand Posture) in Yoga Practitioners

*Ophthalmology* 2006; 113:1327-1332.

**Conclusion:** There was a uniform 2-fold increase in the IOP during Sirsasana, which was maintained during the posture in all age groups irrespective of the ocular biometry and ultrasound pachymetry. We did not demonstrate a higher prevalence of ocular hypertensives in this cohort of yoga practitioners nor did the risk factors contributing to glaucoma show any correlation with magnitude of IOP raise during the posture.

Nocturnal IOP and Glaucoma

- Most individuals spend 1/3rd of day asleep in recumbent position
- Habitual IOPs of most untreated glaucomas higher during nocturnal/sleep period than office hours
  - IOP measured sitting during day and supine position at night
- Important to understand and recognize this
  - May explain why glaucomatous damage occurring in certain individuals

IOP is Positional

“New” Risk Factors

24 Hour IOP

Fluctuation of IOP

Ocular Perfusion Pressure

i

Our Understanding of Diurnal and Nocturnal IOP Has Been Expanded By Recent Studies

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IOP Is Higher At Night

Both healthy eyes and eyes with glaucomatous changes have higher nocturnal supine IOP than diurnal sitting IOP.


How to Measure Nocturnal IOP

- Pneumatonometer:

Sleep in Head Up Position

New Risk Factors to Consider in Glaucoma:

Ocular Perfusion Pressure
- definitions
- clinical studies
- impact of topical medications
Ocular Perfusion Pressure

- The differential between arterial BP and IOP
  - Ocular perfusion is regulated to maintain constant blood flow to the optic nerve despite fluctuating blood pressure and IOP
  - The major cause of reduced blood flow is thought to be secondary to vascular dysregulation in susceptible patients, resulting from abnormal auto-regulation
    - Adjustment of blood flow into anterior optic nerve in response to changes in BP and IOP

Ocular Perfusion Pressure (OPP): Terminology

- OPP – Ocular Perfusion Pressure
- SPP – Systolic Perfusion Pressure
- DPP – Diastolic Perfusion Pressure
- MPP – Mean Perfusion Pressure

OPP and Glaucoma: Hemodynamics

- SPP = SBP – IOP
- DPP = DBP – IOP
  - easiest to use, good evidence
- MPP = 2/3 mean arterial pressure – IOP
  - Arterial Pressure = DBP + 1/3 (SBP – DBP)
  - May best reflect perfusion physiology
**Glaucoma: Non-IOP Mechanisms**

**OPP and Glaucoma: Impact of IOP and BP**


**OPP and Glaucoma: Population Studies**

<table>
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<td>Caucasian</td>
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<tr>
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<td>African-Caribbean</td>
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<tr>
<td>Proyecto Ver</td>
<td>Hispanic</td>
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<tr>
<td>Los Angeles Latino Eye Study (LALES)</td>
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**The Baltimore Eye Survey**

- Cross sectional study of African Americans and Caucasians in Baltimore, MD.
- Lower OPP strongly associated with prevalence of primary open angle glaucoma (POAG).
- Six-fold excess of POAG in subjects with lowest category of OPP.


**Evidence Supporting Role of OPP in Glaucoma**

- Clinical studies
- Epidemiologic studies
  - Cross sectional and cohort
- Clinical trial cohort

**DOPP: Proyecto Ver**

- Cross-sectional study of Hispanics in Nogales and Tucson, AZ.
- Found lower DPP associated with increased risk of POAG.
- DPP ≤50 mmHg, the prevalence of glaucoma rapidly increases linearly

Los Angeles Latino Eye Study: Ocular Perfusion Pressure
- Cross-sectional study of 6,357 Latinos, >40 years in Los Angeles, CA.
- Persons with low diastolic and systolic perfusion pressures had a higher risk of POAG.
- DOPP <50 mmHg, the prevalence of glaucoma rapidly increases linearly.

Studies Summary
- These large studies provide **strong evidence among different populations** for the relationship between vascular deficits and the prevalence, incidence and progression of glaucoma
- Some Limitations,
  - no direct measure of ocular blood flow
  - Varied definitions of hypertension

OPP and Glaucoma: Newest Evidence
- Barbados Eye Study (BES):
  - 9-Year Risk Factor Study
- The Early Manifest Glaucoma Trial (EMGT):
  - Predictors for Long-term Progression

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

Barbados Eye Study: 9-Year Follow-Up

Nocturnal Hypotension and OPP
- Low blood pressure (BP) at night, coupled with high IOP in supine position, compromise OPP.
  - Up to 50% of patients with HTN
  - Using systemic BP meds in the AM to minimize nocturnal hypotension makes sense.
- Using IOP lowering drugs that lower IOP while sleeping makes sense.
  - Avoiding IOP meds that LOWER systemic BP at night (beta blockers, alpha agonists) makes sense.
Glaucoma and oxidative stress: The Basics

- Free radicals cause damage to retinal ganglion cells and their axons
  - Ganglion cell mitochondria are most vulnerable to oxidative stress in glaucoma

- Free radicals also likely cause damage to trabecular meshwork
Ischemia

- Ischemia can activate the astrocytes at the optic nerve head
- This upregulates Nitric Oxide Synthase (NOS-2)
- NOS-2 produces nitric oxide in the vascular endothelial cells
- NO is a vasodilator

Vascular Supply and glaucoma

- Ischemia directly increases the susceptibility of the optic nerve to glaucomatous damage
- Hypotension is a recognized risk factor in glaucoma

Sustained reduced OBF vs dysregulation

- Sustained mild reduced OBF can be compensated for
  - Acute and severe reduced OBF causes AION with a completely different ONH appearance

WAIT - ISN’T VASODILATION A GOOD THING, TO RE-PERFUSE THE TISSUE?
Autoregulation of ocular blood flow

Nocturnal variation in BP

www.als.ca

Blood pressure (mmHg)

10 12 14 16 18 20 22 2 4 6 8 10

Time (hour)

Nocturnal variation in BP

Autoregulation of ocular blood flow

Blood flow

Autoregulation Range

Hyperten

Normal

Perfusion pressure

Blood pressure (mmHg)

Heart rate (BPM)

20 18 16 14 12 10 8 6 4 2 0

Time (hour)

2 4 6 8 10

12 14 16 18 20 22 2 4 6 8 10

Time (hour)

Semmes-Weinstein monofilaments

Glaucoma vs. Normal 24-Hour IOP (Habitual Position)

IOP (mmHg)

Wake

Sleep

Wake

IOP (mmHg)

3:00 a.m.

5:00 a.m.

7:00 a.m.

9:00 a.m.

11:00 a.m.

1:00 p.m.

3:00 p.m.

5:00 p.m.

7:00 p.m.

9:00 p.m.

11:00 p.m.

1:00 a.m.

2:00 a.m.

3:00 a.m.

4:00 a.m.

5:00 a.m.

6:00 a.m.

Blood flow

Autoregulation Range

Hyperten

Normal

Perfusion pressure

www.als.ca
What causes PVD?
- Imbalance between the local factors influencing vasoconstriction and vasodilation
- Small vessels at ONH and retina lack autonomic regulation
- NO
- ET-1

Endothelin-1 and Nitric Oxide
- Both are abnormal in aqueous, vitreous, and serum of glaucoma patients
- The ischemia/reperfusion process is dysfunctional, with delayed and overexaggerated responses in producing ET-1 and NO locally

ONOO- in the eye
- Apoptosis
- Lipid peroxidation
- Protein oxidation
- Inactivation of enzymes
- Tissue necrosis
- Upregulation of MMP’s
- Upregulation of VEGF
- May play a critical role in uveitis
- Damages endothelial cells

Trabecular meshwork changes
- Free radicals contribute to degeneration of TM
  - Alters aqueous outflow
  - Increases IOP
- Glaucoma patients have reduced levels of antioxidants in the anterior chamber
Which came first, the free radical or the high IOP?

Izzotti and colleagues, University of Genoa, Italy

More importantly, how can we fix it?

- Adequate magnesium intake
- Adequate diet rich in antioxidants
- Diet rich in fatty fish (omega-3)

Antioxidants

- Polyphenols – “scavenge” for free radicals
  - neutralize the ROS
  - Green and black tea
  - Red wine
  - Dark chocolate
  - Coffee
- Vascular “regulators”
  - Ginkgo biloba
  - Magnesium
  - Salt???

So what is the underlying cause for these mechanisms?

- Genetic defects in manufacturing natural antioxidants?
- Genetic defect in mitochondrial behavior?
- Genetic or environmental defects in ET-1 and NO synthesis?
- Dietary deficiency?

Coffee

- Contains MCP \(\rightarrow\) selective scavenger of peroxynitrite (ONOO-).
Antioxidants

- Ubiquinone (CoQ10)
  - Ubiquinone is ubiquitous
    - Found in every cell in the body
    - Naturally occurring enzyme
  - Acts primarily at inner mitochondrial enzyme complexes to assist cells in energy production
  - Prevents lipid peroxidation and DNA damage induced by oxidative stress

Antioxidants - Ginkgo

- Ginkgo biloba extract (GBE)
- Most widely prescribed medication in Germany
  - Depression
  - Impotence
  - Infertility
- Initially marketed as a memory-aid supplement in the U.S., OTC

GBE effects on blood flow

- GBE improves peripheral, cerebral and ocular blood flow
  - 23% increase OBF with 2 days of treatment
    - 40 mg/3 times a day
    - No effects BP, HR, IOP
- Decreases blood viscosity – caution!

Ginkgo: summary

- Recommended dose 120 mg/day
- Powerful antioxidant capable of acting at ganglion cell mitochondria
- Inhibits nitric oxide and superoxide
- Increases glutathione
- Inhibits PAF activity
- Decreases lipid membrane peroxidation
- Protect virtually all the cells and pathways involved in the retina and ONH

GBE chemistry

- GBE scavenges superoxide and nitric oxide

Black currant anthocyanins

- Several studies show normalization of serum ET-1 in patients with glaucoma
Magnesium
- May enhance vascular regulation
- Appears to reduce the vasoconstrictive effects of ET-1
- Recommended dose 300 mg/day

Calcium channel blockers?
- "Classical anti-vasospastic drugs"
- Reduce effect of ET-1
- Low dose to avoid decreased BP

Steigerwalt et al, 2008
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2447819/
- 160 mg Mirtoselect
- 80 mg Pycnogenol

Steigerwalt et al, 2010
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2447819/
- 80 mg Mirtoselect
- 40 mg Pycnogenol
- 1gtt Latanoprost
The Results - IOP

- Increases systolic blood flow 39 % Increase
- Increases diastolic blood flow 192 % Increase
- Decreases intraocular pressure 40 % Decrease

120 mg of Mirtogenol costs about $1/day

Summary of Facts

Case WS

- 75 yo male
- + HTN w/ multiple BP meds x 20+ yrs
  - 105/68 in office
  - 5’5”, 142 lbs
- CCT= 532µ
- Initial IOP 23 mmHg
  - Now repeatedly 11-13 mmHg over 5+ years
- Current Medication:
  - PGA
- Good compliance and follow up
Q = What is the Explanation?
Compliance?
Other Potential Risk Factors:
- 24 Hour IOP
  - IOP of 12 mmHg @ 2PM = ?? @ 2AM ~ 18 mmHg
- DOPP
  - DBP of 68 mmHg @ 2PM = ?? @ 2AM ~ 58 mmHg
  - ? DOPP @ 2AM = 58 - 18 = 40 mmHg
Case WS

- Is there anything else that can be done?
- **Possibly:**
  - Offer Nocturnal IOP control
  - Offer Improved DOPP

**Add a CAI BID**

Letter to PCP, explain OPP and Low BP related Risk

? Adjust BP Meds

Summary: OPP and Glaucoma Progression

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

Obstructive Sleep Apnea and Glaucoma
OSA – Etiology
- Recurrent episodes of collapse of the pharyngeal airway
- Leads to decrease in oxygen saturation, swings in heart rate, arousal from sleep
- May occur hundreds of times each night

OSA – Daytime Symptoms
- Sleepiness
- Chronic fatigue
- Decreased cognition

OSA and The Eye
- Associations:
  - Glaucoma
  - NAION
  - Papilledema
  - Floppy eyelid syndrome

Sleep Apnea: Association
- 0% (0 of 2) - younger than 45 years,
- 50% (3 of 6) - 45–64 years,
- 63% (5 of 8) - older than 64 years
- Inquire about in high risk patients.

Sleep Apnea: Not a Risk Factor
- Conclusions: This nested case-control study does not support a large impact of sleep apnea on the eventual development of glaucoma relative to other putative risk factors.

Sleep Apnea: No Relation to Glaucoma
- The Association between Glaucoma and Other Causes of Optic Neuropathy and Sleep Apnea
  - RESULTS: Among the 2,299,981 individuals in the study, 166,346 (6.9%) had 1 or more sleep apnea diagnoses. The hazard of open-angle glaucoma was no different among persons with sleep apnea either treated (adjusted hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.82 to 1.18) or untreated with continuous positive airway pressure (HR, 1.01; 95% CI, 0.89 to 1.13) and individuals without sleep apnea. Similar findings were observed when assessing the hazard of normal-tension glaucoma developing (P > .05 for both comparisons). A signifi-
Brimonidine Neuroprotective?

Overview:
- to compare brimonidine to timolol maleate in preserving visual function in low-pressure glaucoma
  - randomized, double-masked, multicenter clinical trial
- Outcome
  - Low-pressure glaucoma patients treated with brimonidine who do not develop allergy are “less likely to have field progression than patients treated with timolol.”
  
  – AJO Mar 2011

Issues with Data/Conclusions

- Failure rate of beta blockers
  - much higher than our collective clinical experience: EMGT, OHTS
  - Extrapolating the Kaplan-Meier survival graph to 5 years would predict a 100% progression rate for the patients taking timolol
- Side effect rate of brimonidine
  - ~30 % drop out due to side effects (0.2%)
- Degree of IOP lowering in treatment groups
  - Approximately the same between the 2 drugs

No Nocturnal IOP Lowering with Brimonidine 0.1% TID


Cerebrospinal Fluid Pressure


- The trans-lamina cribrosa pressure difference (and not the trans-corneal pressure difference, i.e. the IOP) is of most importance for the physiology and pathophysiology of the ONH

Cerebrospinal Fluid Pressure


- The trans-lamina cribrosa pressure difference (and not the trans-corneal pressure difference, i.e. the IOP) is of most importance for the physiology and pathophysiology of the ONH
- Studies suggest a physiological association between the pressures in all 3 fluid filled compartments, i.e. the systemic arterial BP, the CSF pressure and the IOP
- Low CSF pressure may play a role in the pathogenesis of NTG
A pressure imbalance between the two circulating fluids of the nervous system may be the cause of glaucomatous damage to the optic nerve.

The ICP is lower than normal in POAG and NTG and elevated in OHT.

Findings suggest that an elevated ICP in OHT may counterbalance the high IOP, thus potentially preventing or slowing glaucomatous damage to the optic nerve.

Conversely, a reduced ICP in patients with NTG may increase their risk of developing glaucoma.

CONCLUSION:

- Some ocular hypertensive subjects with increased intraocular pressure measurements (after correction for their dependence on central corneal thickness) had an abnormally high lumbar cerebrospinal fluid pressure.

- The elevated retro-lamina cribrosa pressure may have led to a normal trans-laminar pressure difference in the eyes with elevated intraocular pressure, so that glaucomatous optic nerve damage did not develop.

Questions to address

- Do all POAG patients have low CSF?
- Conversely do all patients with low CSF develop POAG?
- Does CSF pressure measured by lumbar puncture represent CSF pressure in the optic nerve subarachnoid space?
  - Is the optic nerve subarachnoid space CSF Pressure really low in POAG?
- How would we diagnose and treat POAG patients in context of a low CSF?
  - Is there any non-invasive method to explore the orbital CSF pressure?

Other lifestyle considerations in glaucoma

- Yoga – inverted postures detrimental based upon currently available evidence
  - 7 PubMed papers RE Sirsasana
- Aerobic exercise – seems to lower IOP
  - High variability among studies
Controversial topics in lifestyle-associated glaucoma management

- Stress reduction
- Meditation
- Cold avoidance
- Dietary supplementation
- Avoid dramatically low body weight/fat
- Avoid major fasting periods

Mechanism of Glaucoma has gotten complicated:

Summary

- What to do Now:
  - Measure IOP much more frequently.
  - Consider situations of low IOP:
    - Thin Central Corneal Thickness.
  - Record Medical History and Systemic Medications
  - Measure Blood Pressure, Calculate Ocular Perfusion Pressure.