Thinking Outside the Box with Normal Tension Glaucoma:

Optometry's Role in Modifiable Risk Factors

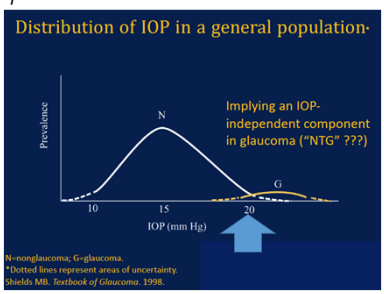
Dr. Beth Steele
UAB School of Optometry

Lecture Objectives

- Review what we know
- Speculate new thoughts on disease
- Update on diagnostic tools
- Optometry's role in modifiable risk factors
- Other recommendations?

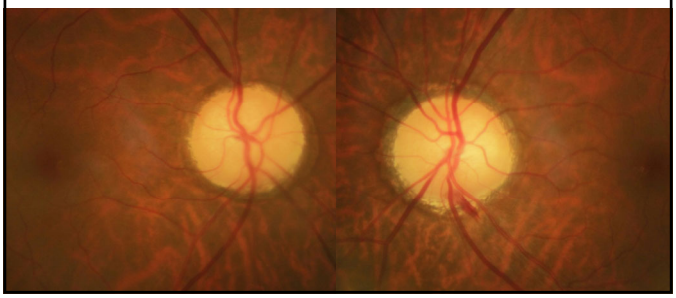
20% of newly diagnosed glaucoma patients have IOP < 21 mm Hg at presentation

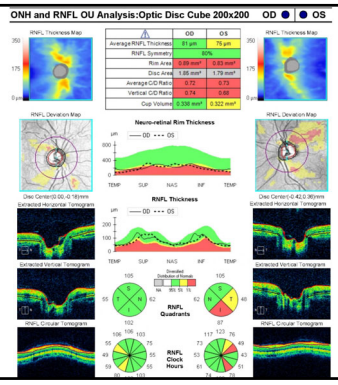
- Increased Risk of NTG
  - FHx NTG
  - Japanese ancestry
  - Female
  - Lower CCT

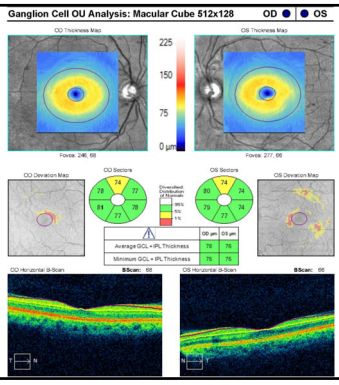


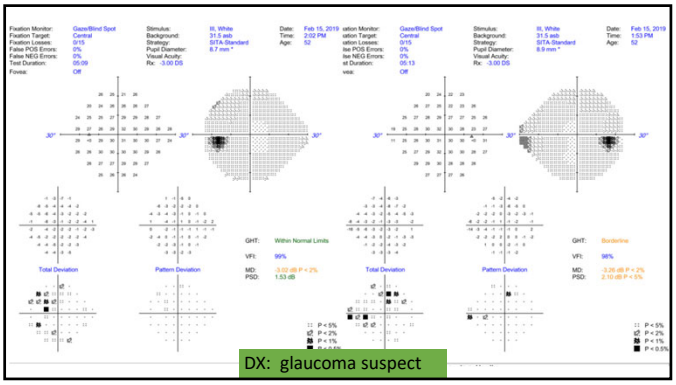
Beaver Dam Eye Study

46 year old Japanese male
IOPs - 12









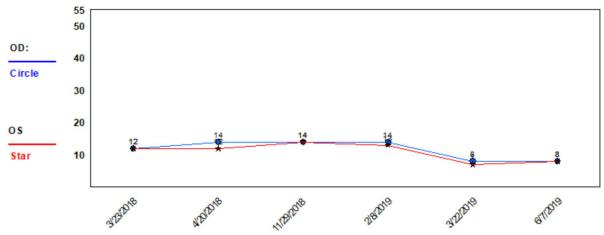
DX: glaucoma suspect

1 year later…

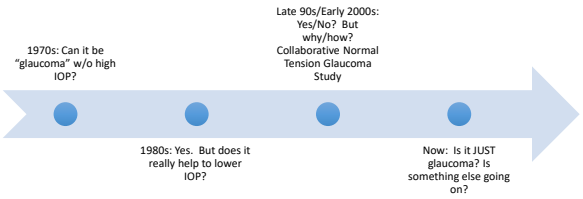
- Another drance heme, right eye at 5:00
- VF: mild defect consistent with glaucomatous loss that corresponds to RNFL/disc appearance

DX: normal tension glaucoma
Treatment: brimonidine BID OU

Max IOP = 14mmHg
Treated IOP = 8mmHg



History of the clinical approaches on NTG:



Collaborative Normal Tension Glaucoma Study

- ***Does lowering IOP by 30% reduce progression in patients with NTG?***

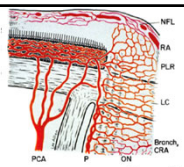
- Treatment Group:
  - Lower IOP by 30%
  - Avoided beta blockers and alpha agonists
  - Included ALT or Trab
  - Endpoints: Progression of either VF or ONH appearance
- Findings:
  - 30% reduction in IOP slows progression in NTG
    - *But by unknown mechanisms*
    - *Secondary analyses show no effect*
  - 65% of the untreated group did not progress in 5 years
  - Treated group had greater cataracts surgery (38% vs 11%)
  - Risk Factors identified: Females, migraine, disc hemorrhage

Am J Ophthalmol. 1998

What is it, and why does it happen?

- **Sub-set of POAG, or its own disease?**
  (i.e. lump or split?)
  - Risk factors / associated factors are different
  - Reducing IOP - not as important in disease progression ?

1. **Vascular theory**
2. **Mechanical theory**



Vascular Theory of Glaucoma: Changes in Ocular Blood Flow

1. Decreased Perfusion pressure at disc
2. Poor Autoregulation of vascular system

Vascular dysregulation
Increased vascular resistance
Increased blood viscosity
Reduced blood flow

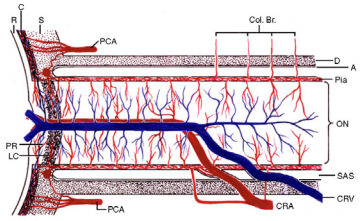
Reduced Blood Flow to ONH in Glaucoma (*could be*)….

1. …as a result of high IOP, after subsequent RNFL and RGC loss
2. OR …along with IOP, causes RNFL and RGC loss
3. OR …independent of IOP, leading to RNFL and RGC loss

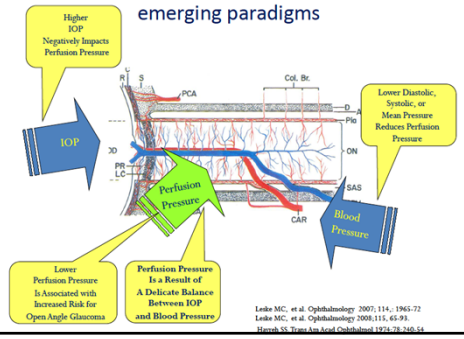
→ *may involve both retinal and choroidal circulatory systems,* ***VF loss being the ultimate consequence….***

Blood supply to ONH

- Anatomy
  - Short Posterior Ciliary a's ← Ophth a.
  - Choroidal a's – contribute to prelaminar and laminar ONH
  - Pial a's – laminar and retrolaminar ONH
- Physiology ….
  Blood flow , AND
  Autoregulation of ONH and Retina



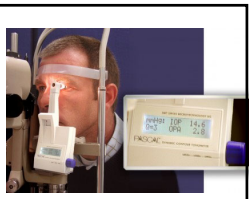
Ocular Perfusion Pressure & Glaucoma Progression – emerging paradigms

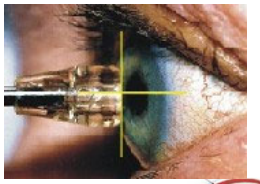


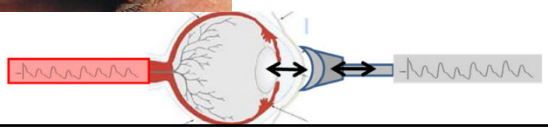
Slide courtesy of Dr. Leo Semes

Leske MC, et al. Ophthalmology 2007; 114.; 1965-72
Leske MC, et al. Ophthalmology 2008;115, 65-93.
Hayreh SS. Trans Am Acad Ophthalmol 1974;78:240-54

Ocular Blood Flow Analyzers?

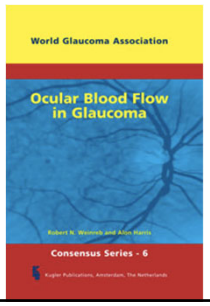






Consensus Statement of WGA, 2009

- *"A comprehensive approach, utilizing multiple imaging technologies is required for meaningful insight into the multiple vascular beds of the eye."*
- Currently no SINGLE blood flow imaging device is capable of evaluating ocular blood flow relevant to glaucoma.



Ocular Perfusion Pressure (OPP)

- ***OPP = balance between IOP and BP = Mean Arterial Pressure – IOP***
- Low OPP associated with↑ POAG
- ↓ed blood flow reported in retina, ONH, choroid and retrobulbar vasculature in glaucoma


Ocular Perfusion Pressure as a Risk Factor


BMC Ophthalmology
Ocular perfusion pressure and ophthalmic artery flow in patients with normal tension glaucoma

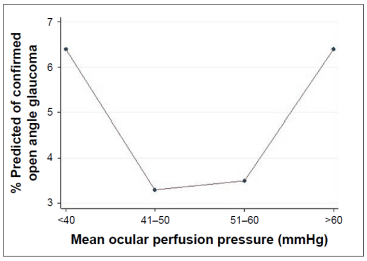

BioMed Research International
Volume 2015, Article ID 308505, 7 pages
http://dx.doi.org/10.1155/2015/308505
Review Article
Ocular Blood Flow and Normal Tension Glaucoma
Ning Fan,[1] Pei Wang,[2] Li Tang,[2] and Xuyang Liu[1]

Hafez, Leske 2015.
Leske MC et al. Ophth, 2008.

Mean Arterial Pressure: Using BP to assess ocular blood flow

- MAP = 2/3 DBP + 1/3 SBP
- OPP is reduced with….
  - High IOP
  - Low MAP (DBP or SBP)
- OPP = MAP – IOP
  - *Too low when OPP <40*

- Increased risk of glaucoma with both *high and low* OPP
- ≈Double the risk with:
  - **High DBP (>90)**
  - **Low OPP (<40)**
  - **Low DBP (<60)**
- *Diastolic perfusion pressure* – strongly correlates with severity of VF and structural glaucoma progression



Cantor E, et al. Clin Ophth 2018.

Vasospasm

- 11-19% of the population have some sort of vasospasm
  - Raynaud's
  - Migraine
  - ….
- Often… an imbalance between nitric oxide and endothelin
- *Primary Vascular Dysregulation*: Oxidative stress and ischemia due to periodic vasoconstriction / reperfusion
  - Flammer syndrome
- ➔ glaucomatous VF loss

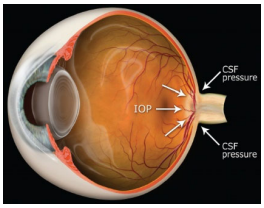
Gramer G et al. IOVS 2015.

Vascular Dysregulation

- Primary – *major risk of glaucomatous optic neuropathy*
  - Females, Japanese, academics (vs. blue collar)
  - Diagnosis based on history alone
  - Impacts autoregulation
  - Unstable – reperfusion leads to oxidative stress
- Vs. Secondary
  - From connective tissues diseases such as RA, SLE, Crohn's, MS
  - Increase in endothelin
  - Reduces blood flow but *does not* typically impact autoregulation

Greishaber MD et al. Survey of Ophth 2007.
Gramer G et al. IOVS 2015.

Mechanical Theory of Glaucoma via ICP

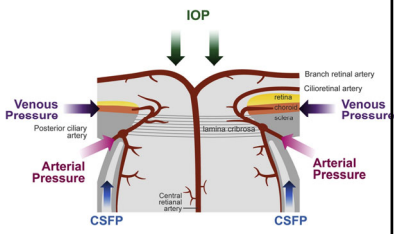


1. Mechanical – higher translaminar pressure (TLP)
2. (Flow dynamics)

Boye D, et al. Clin Exp Ophth 2018.
Pircher A, et al. Acta Ophth 2018.

Mechanical: Translaminar Pressure Gradient (TLPG)

- Balance of IOP and ICP
  - Anterior vs. posterior pressure at lamina
- Normal – 4mmHg posterior-directed pressure
- Increased posteriorly – directed TLP caused by decreased ICP

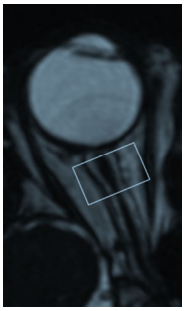


Ren R et al Ophth 2010
Berdahl JP et al. Ophth 2008.
Roy Chowdhury, IJ 2015
Jonas JB, et al. Invest Ophth Vis Sci 2003

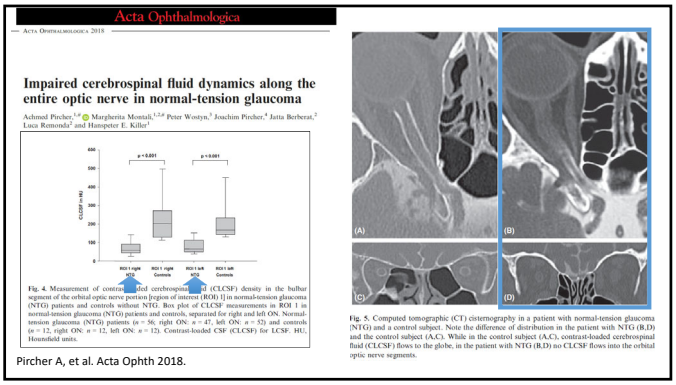
Suh MH. Survey of Ophth 2014.

Impaired CSF Flow Dynamics?

- ***Build up of neurotoxic substances in subarachnoid space***
- NTG patients with narrower optic canal and narrower SAS
  - Bottleneck of CSF
- Lack of rapid CSF turnover which is crucial for brain and ON function



Boye D, et al. Clin Exp Ophth 2018.
Pircher A, et al. Acta Ophth 2018.



Acta Ophthalmologica

Acta Ophthalmologica 2018

Impaired cerebrospinal fluid dynamics along the entire optic nerve in normal-tension glaucoma

Achmed Pircher,[1,2] Margherita Montali,[1,2,3] Peter Wostyn,[3] Joachim Pircher,[4] Jutta Berberat,[2] Luca Remonda[5] and Hanspeter E. Killer[1]

Fig. 4. Measurement of contrast-loaded cerebrospinal fluid (CLCSF) density in the bulbar segment of the orbital optic nerve portion [region of interest (ROI) 1] in normal-tension glaucoma (NTG) patients and controls without NTG. Box plot of CLCSF measurements in ROI 1 in normal-tension glaucoma (NTG) patients and controls, separated for right and left ON. Normal-tension glaucoma (NTG) patients ($n = 56$; right ON: $n = 47$, left ON: $n = 52$) and controls ($n = 12$, right ON: $n = 12$, left ON: $n = 12$). Contrast-loaded CSF (CLCSF) for LCSF. HU, Hounsfield units.

Fig. 5. Computed tomographic (CT) cisternography in a patient with normal-tension glaucoma (NTG) and a control subject. Note the difference of distribution in the patient with NTG (B,D) and the control subject (A,C). While in the control subject (A,C), contrast-loaded cerebrospinal fluid (CLCSF) flows to the globe, in the patient with NTG (B,D) no CLCSF flows into the orbital optic nerve segments.

Pircher A, et al. Acta Ophth 2018.

Course, and Management of Modifiable Risk Factors

Progression in NTG

- Slow but varies
  - No change at all *for some* at 5 years
- Higher risk and faster progression…
  - Females
  - Migraine
  - Disc hemorrhages

Vascular etiology? Dysregulation…??

IOP – Yes?

Natural History of Normal-Tension Glaucoma

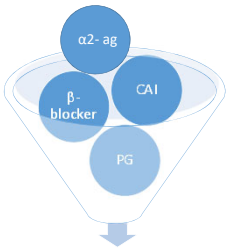
Collaborative Normal-Tension Glaucoma Study Group

- Reducing IOP by 30% in NTG ↓s progression of VF defects
  Collaborative Normal Tension Glaucoma Study (CNTGS), Ophthal 2001
  Early Manifest Glaucoma Trial (EMNGT)
  (but limitations in the study….)
- Larger the IOP reduction = lower progression rate
  - Maintaining reduced pressure helps to ↓VF loss in NTG over a 15 yr period
  - But can long-term progression be completely stopped? **We don't know.**

Ole S, et al. Japan J Ophth, 2017.

Topical Drugs of Choice?

- IOP-lowering effect
  - Traditional approaches
  - Avoid?
    - Non selective β-blocker: vasoconstriction
- Neuroprotective effect ?
  - α2- agonists



Which is best?

Review: Vascular Impact of β-blockers

- "non-selective" – block both β1 and β2
- "selective" – only block β1

RECEPTOR TYPE	ORGAN	ACTION
β1-receptors	Heart	Increased HR
	Kidney	Renin release
β2-receptors	Lungs	Bronchodilation
	Blood vessels	Vasodilation
	Smooth muscle	Relaxation
	Eye	CB: aqueous production

Impact on vasculature…, OPP?

- B-blockers
- Alpha2 agonists
- Prostaglandins ?

Ophthalmology

Topical medical therapy and ocular perfusion pressure in open angle glaucoma: a systematic review and meta-analysis

George Rennie ✉, Angus Wilkinson, Andrew White, Marinella Ruospo, Armando Teixeira-Pinto & Giovanni Strippoli

Conclusions: We identified low to moderate quality evidence describing post-intervention mean ocular perfusion pressure in open angle glaucoma. Bimatoprost increases mean ocular perfusion pressure when compared to timolol. As a class, prostaglandins increase mean ocular perfusion pressure. Prostaglandins may provide beneficial ocular perfusion pressure profiles compared to alternative agents.

Beta-Blockers?

- NON-SELECTIVE Beta-blockers: Significant additional precaution
  - Vs. β1 - only
- Topical β-blockers administered at night to those taking systemic β-blockers may reduce perfusion to the ONH plus β -blocker therapy to
  - reducing IOP is ineffective at night anyway…
- *Which brings us to . . .(a Leo Semes question…)*

Hayreh SS. Effect of nocturnal blood pressure reduction on retrobulbar hemodynamics in glaucoma. Graefes Arch Clin Exp Ophthalmol. 2002; 240: 867-8.

- Is glaucoma AION that happens over a lifetime?

OR

- Is AION glaucoma that happens overnight?

Alpha 2 agonists: Neuroprotection
Possible mechanisms – many but conflicting data

- Brimonidine - highly selective alpha2 agonist
  - Inhibits NMDA receptor → ↓ing glutamate
- Others potentials….
  - Memantine – NMDA receptor antagonist
    - Effective when excessive levels of glutamate are present
    - Shown to protect RGCs in several animal models – not in humans
  - Neurotrophins – suppress apoptosis signal
  - TGF-α

Rho-kinase inhibitors and neuroprotection

- *Systemically*, suggested value in MI, HTN, kidney disease, neurologic disease (e.g. Alzheimer's, MS…)
- Netarsudil for glaucoma…
  - ↑ optic nerve blood flow
  - Interrupts RGC apoptosis
  - Axon regeneration
- Lowers IOP by…
  - TM outflow
  - Production of aqueous
  - Reduction of EVP


Current Ophthalmology Reports
June 2018, Volume 6, Issue 2, pp 86–92 | Cite as
New Technology and Current Understanding of Episcleral Venous Pressure
Authors Authors and affiliations
Michael Greenwood ✉, John Berdahl, Mitch Ibach

Episcleral Venous Pressure – Role in Treatment?


Current Ophthalmology Reports
June 2018, Volume 6, Issue 2, pp 86–92 | Cite as
New Technology and Current Understanding of Episcleral Venous Pressure
Authors Authors and affiliations
Michael Greenwood ✉, John Berdahl, Mitch Ibach

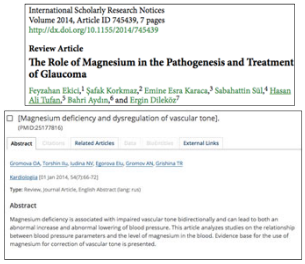
- Increase in EVP = increase in IOP
- "Normal" EVP by venomanometry = around 7-9
- IOP = *(Q – U)/c* + EVP
  - *Q* is the aqueous flow rate
  - *U* is the pressure-insensitive uveoscleral outflow rate
  - *c* is the outflow facility

ANYTHING that causes BP to fluctuate….

Abnormal autoregulation
Vasospasm
Nocturnal Hypotension
Medication changes

Vascular Dysregulation

- Primary – *major risk of glaucomatous optic neuropathy*
  - Magnesium helps to regulate vascular tone
  - Calcium, phosphorous …
- Vs. Secondary
  - Treat underlying condition


International Scholarly Research Notices
Volume 2014, Article ID 745439, 7 pages
http://dx.doi.org/10.1155/2014/745439
Review Article
The Role of Magnesium in the Pathogenesis and Treatment of Glaucoma
Feyzahan Ekici,[1] Şafak Korkmaz,[2] Emine Esra Karaca,[3] Sabahattin Sül,[4] Hasan Ali Tufan,[5] Bahri Aydın,[6] and Ergin Dilekör[7]

[Magnesium deficiency and dysregulation of vascular tone]. (PMID:25777816)
Abstract Citations Related Articles Data Bookshelves External Links
Gromova OA, Torshin IIu, Sudina NV, Egorova EIu, Gromov AN, Grishina TR
Kardiologiia [01 Jan 2014, 54(7):66-72]
Type: Review, Journal Article, English Abstract (lang: rus)
Abstract
Magnesium deficiency is associated with impaired vascular tone bidirectionally and can lead to both an abnormal increase and abnormal lowering of blood pressure. This article analyzes studies on the relationship between blood pressure parameters and the level of magnesium in the blood. Evidence base for the use of magnesium for correction of vascular tone is presented.

Greishaber MD et al. Survey of Ophth 2007.
Gramer G et al. IOVS 2015.

Migraine


Migraine and Vasospasm in Glaucoma: Age-Related Evaluation of 2027 Patients With Glaucoma or Ocular Hypertension
Gwendolyn Gramer,[1] Bernhard H. F. Weber,[2] and Eugen Gramer[3]

- Known to cause a temporary decrease in ocular blood perfusion
- Females (…like vasospasm, ….like NTG)
- Frequently reported association with glaucoma
  - ↑ed incidence of NTG vs. POAG
- Associated with Raynaud's, connective tissue disease
- Why?
  - Perhaps Migraine, Raynaud's, vasospasm, ….*and NTG*…. Are expressions of a vasospastic disorder?
  - Possible genetic link

Nocturnal Hypotension

- Magnitude and duration – consistent with risk of NTG and progression
  - "extreme dippers" – higher risk
  - Diastolic dip – higher risk
- Blood flow measurements could guide changes in treatment

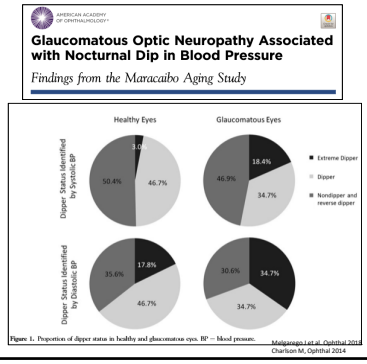

AMERICAN ACADEMY OF OPHTHALMOLOGY
Glaucomatous Optic Neuropathy Associated with Nocturnal Dip in Blood Pressure
Findings from the Maracaibo Aging Study

Figure 1. Proportion of dipper status in healthy and glaucomatous eyes. BP = blood pressure.
Malgorzago I et al. Ophthal 2014
Charlson M, Ophthal 2014

HEART HEALTH › TREATMENT

The Best Time to Take Blood Pressure Medication

Morning Versus Evening Administration of a Calcium Channel Blocker in Combination Therapy for Essential Hypertension by Ambulatory Blood Pressure Monitoring Analysis

Chih-Sheng CHU,[1] MD, Kun-Tai LEE,[1] MD, Shih-Hun CHEN,[1] MD, Ye-Hsu LU,[1] MD, Tsung-Hsien LIN,[1] MD, Wen-Chol VOON,[1] MD, Sheng-Hsiung SHEU,[1] MD, *and* Wen-Ter LAI,[1] MD

ACE Inhibitor Heart Drugs Best Taken At Bedtime, Study

By Catharine Paddock, Ph.D. | Published Wednesday 11 May 2011

Many doctors recommend their patients take heart drugs in the morning with their breakfast, but a new study from Canada suggests that one group of drugs, angiotensin-converting enzyme (ACE) inhibitors, works best when taken at bedtime because they reduce the effect of a hormone that is most active during sleep.

Time of administration important? Morning versus evening dosing of valsartan

Dion H. Zappe[a], Nora Crikelair[a], Albert Kandra[b], and Paolo Palatini[c]

Conclusion: Once-daily dosing of valsartan 320 mg results in equally effective 24-h BP efficacy, regardless of dosing time.

J Hypertension 2015

Sleep Apnea Syndrome/Obstructive Sleep Apnea (SAS / OSA)

- 14-49% middle aged men in US and Europe
- Higher prevalence of glaucoma among patients with SAS
  - 11-27% of patients !
  - Worse with moderate to severe SAS
  - Higher rate of NTG in particular
  - Higher rate of progression

Prevalence and risk factors of eye diseases in adult patients with obstructive sleep apnoea: results from the SLE.E.P.Y cohort study

BMJ 2014

Emilio Pedrotti,[1] Christian Luigi Demasi,[1] Enrico Bruni,[1] Francesca Bosello,[1] Paolo Plinio Di Sarro,[1] Mattia Passilongo,[1] Adriano Fasolo,[1,2] Nicola Gennaro,[3] Alessandra De Gregorio,[4] Marcello Ferrari,[5] Giorgio Marchini[1]

Obstructive Sleep Apnea and Increased Risk of Glaucoma

Ophthalmology 2013

A Population-Based Matched-Cohort Study

Ching-Chan Lin, MA,[1] Chao-Chien Hu, MD,[2,3,4,5] Jau-Der Ho, MD, PhD,[2,3] Hung-Wen Chiu, PhD,[1] Heng-Ching Lin, PhD[1,*]

Clin Exp Ophth 2008
J Glaucoma 2011
Graefes 2011
Sergi M et al. J Glaucoma 2007

SAS leads to ….

- *…Episodic obstructive respiratory disturbances → severe hypoxemia and increased vascular resistance → compromised ONH perfusion and oxygenation → glaucomatous optic neuropathy*
- Correlation with structural and function loss
  - Glaucoma patients with SAS have a *steeper MD slope*
  - *RNFL thinning* in mod-severe SAS vs. normal
- …Oxidative stress ➔ producing reactive oxygen species
  - CPAP treatment has shown to help

Acta Ophth 2019

Sleeping position?

- 66% of NTG patients with asymmetric VF loss presented a worse eye in their preferred side position
  - ➢*compressive effect?*
  - ➢*reduction in perfusion?*
  - ➢*facial anatomy a consideration?*

Relationship between sleep position and glaucoma progression

Kaplowitz, Kevin[a]; Dredge, Justin[a]; Honkanen, Robert[b]

Current Opinion in Ophthalmology: November 2019 - Volume 30 - Issue 6 - p 484–490

ARVO Annual Meeting Abstract | June 2015

Relationship between Sleeping Position and Asymmetric Visual Field loss in Glaucoma Patients by Quantitative Measurement of Body Position Using a Mobile Device

Sang-Yoon Lee; Jin Wook Jeoung; Dong Myung Kim; Ki Ho Park

Acta Ophthalmologica. 93(4):e313–e314, JUNE 2015

Relationship between preferred sleeping position and unilateral disc haemorrhage in normal-tension glaucoma patients

Kyoung Kim;Ki Park;

Phosphodiesterase 5 inhibitors for ED

- Phosphodiesterase 5 inhibitors for ED
- Impact blood flow to optic nerve
  - Association with AION…related ??
  - Use for ≥1yrs : ↑prevalence self-reported glaucoma
- Impact on IOP ? Not well-established
  - Increase IOP by 1-4mmHg ; short-lived, dose-related
  - Increases blood flow to CB

PLoS One 2017

Risk factors (RF) for atherosclerosis are largely parallel to increased IOP

- ***Age***
- ***Smoking***
- ***Dyslipidemia***
- ***Systemic hypertension***
- ***Male gender***
- ***Obesity***

OPEN ACCESS

Glaucoma | March 2019

Hyperlipidemia, Blood Lipid Level, and the Risk of Glaucoma: A Meta-Analysis

Shiming Wang; Xianyi Bao

- **Therefore reducing these risk factors reduces IOP (some..?)**
  - physical exercise
  - weight loss
  - treatment of dyslipidemia
- **And may increase**
  - blood flow
  - aqueous outflow through the TM

Flammer J, Mozaffariaeh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? 2007. Surv Ohthalmol 52: S162-173.

Nutritional Supplements and Herbals

Just saying….

NTG needs a holistic approach

Omega-3s ?

February 2018

Association of Dietary Fatty Acid Intake With Glaucoma in the United States

Ye Elaine Wang, MD[1]; Victoria L. Tseng, MD, PhD[2]; Fei Yu, PhD[1,2]; et al

> Author Affiliations

JAMA Ophthalmol. 2018;136(2):141-147. doi:10.1001/jamaophthalmol.2017.5702

- Increased *(but not too much!)* intake of EPA/DHA associated with lower likelihood of glaucomatous optic neuropathy
  Wang et al. JAMA Ophth 2018
- *Decrease blood viscosity*
- *Reduces inflammation*

Ginko Boloba

- Reduces peripheral vasospasm, so improves ocular perfusion
- Evidence supporting an increase in OBF
- Neuroprotective
- Anti-oxidant
- Proposed for high-tension glaucoma (Cybulska-Heinrich et al. 2012)
- Requires further investigation

REVIEW

Ginkgo biloba and its potential role in glaucoma

Jessica Minji Kang and Shan Lin

Current Opinion Ophth 2018

Bilberry

- Contains antioxidants: resveratrol, anthocyanins
- Anti-angiogenic properties
- May decrease blood vessel permeability
- **+French Maritime Pine Bark**= Mirtogenol ®
  - Ocular blood flow

Steigerwalt R, et al. Molecular Vision 2008

Nicotinamide *(amide of VitB3)* for mitochondrial health

J Glaucoma. 2017 December ; 26(12): 1161–1168. doi:10.1097/IJG.0000000000000767.

Glaucoma as a metabolic optic neuropathy: making the case for nicotinamide treatment in glaucoma

Pete A Williams, PhD[1], Jeffrey M Harder, PhD[1], and Simon W M John, PhD[1,2]

Abstract

Mitochondrial dysfunction may be an important, if not essential, component of human glaucoma. Using transcriptomics followed by molecular and neurobiological techniques, we have recently demonstrated that mitochondrial dysfunction within retinal ganglion cells is an early feature in the DBA/2J mouse model of inherited glaucoma. Guided by these findings, we discovered that the retinal level of nicotinamide adenine dinucleotide (NAD, a key molecule for mitochondrial health) declines in an age-dependent manner. We hypothesized that this decline in NAD renders retinal ganglion cells susceptible to damage during periods of elevated intraocular pressure. To replete NAD levels in this glaucoma, we administered nicotinamide (the amide of vitamin B_3). At the lowest dose tested, nicotinamide robustly protected from glaucoma (~70% of eyes had no detectable glaucomatous neurodegeneration). At this dose, nicotinamide had no influence on intraocular pressure and so its affect was neuroprotective. At the highest dose tested, 93% of eyes had no detectable glaucoma. This represents a ~10-fold decrease in the risk of developing glaucoma. At this dose, intraocular pressure still became elevated but there was a reduction in the degree of elevation showing an additional benefit. Thus, nicotinamide is unexpectedly potent at preventing this glaucoma and is an attractive option for glaucoma therapeutics. Our findings demonstrate the promise for both preventing and treating glaucoma via interventions that bolster metabolism during increasing age and during periods of elevated intraocular pressure. Nicotinamide prevents age-related declines in NAD (a decline that occurs in different genetic contexts and species). NAD precursors are reported to protect from a variety of neurodegenerative

”Hey, Doc…”

Revisiting Cannabis…

- Historically short term effects
  - Max effect in 60-90 min for 5-8 hours
- Up to 28% decrease in IOP
- Males vs. females
- Selected molecule as CB1 agonist

Canadian Journal of Ophthalmology
Volume 54, Issue 1, February 2019, Pages 7-8

Editorial

Medical use of cannabis for glaucoma

Paul Rafuse MD, PhD, FRCSC *, Yvonne M. Buys MD, FRCSC †

Glaucoma

Δ^9-Tetrahydrocannabinol and Cannabidiol Differentially Regulate Intraocular Pressure

Sally Miller, Laura Daily, Emma Leishman, Heather Bradshaw, and Alex Straiker

IOVS Dec 2018

pharmaceuticals

MDPI

Article

Controlled-Deactivation CB1 Receptor Ligands as a Novel Strategy to Lower Intraocular Pressure

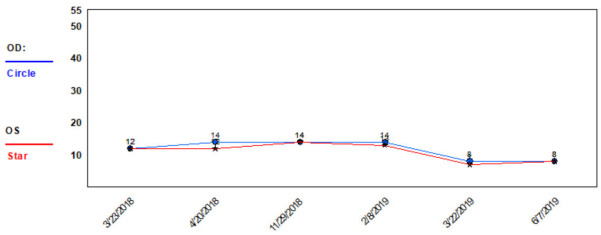
Sally Miller [1], Shashank Kulkarni [2,†], Alex Ciesielski [1], Spyros P. Nikas [2], Ken Mackie [1], Alexandros Makriyannis [2] and Alex Straiker [1,*]

June 2018

2 most active compounds in cannabis

1. THC – known to have an IOP-lowering effect since 1971
   - Confirmed, with many forms
   - Activates CB1 and GPR18 receptors
2. CBD – long considered ***inactive***
   - Zero impact on IOP in 3 studies , but most recently:
   - Can interfere with THC's IOP lowering impact
   - *At equal concentrations, CBD actually eliminates the IOP lowering effect of THC*

Back to our Patient with Treated IOP = 8mmHg



What else can we do?

- Areas of history that we can work with?
  - HTN
  - Hypercholesterolemia
  - Meds
    - Atorvistatin
    - HCTZ
    - Amlopidine
- What time of day does he take his BP meds?
- Does he snore/feel sleepy during the day?
- Suspicion of a blood flow disorder?
- Sleeping position?
- Anything else?

Lifestyle Modifications – Our Role ?

- Sleep study referral
- Blood / primary work-up and regular care
- *Heart Healthy* Diet and habits
  - Exercise
  - Weight loss
  - Smoking Cessation

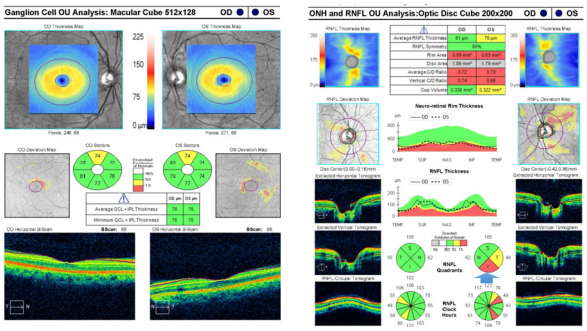
Relationship of lifestyle, exercise, and nutrition with glaucoma

Perez, Claudio I.[a,b]; Singh, Kuldev[c]; Lin, Shan[d]

Current Opinion in Ophthalmology: March 2019 - Volume 30 - Issue 2 - p 82–88

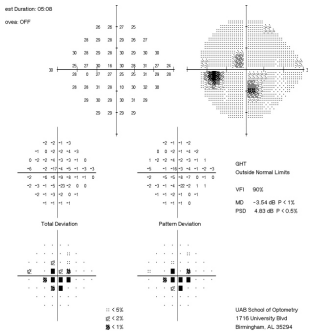
Clinical Pearls in Diagnostic Tools for NTG

Technology teaches us new things every day!



1st ask yourself…

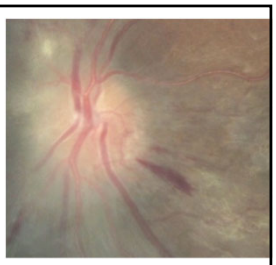
- Is it glaucoma-like loss ?
  - Is it *NTG-like* loss ?
- NTG defects…
  - closer to fixation and deeper
  - Superior arcuate zone – may progress faster
  - > progression compared to HTG



Ganeshrao SB et al. IOVS 2019

Drance Heme

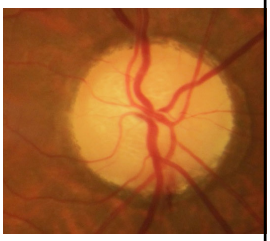
- Not always glaucoma!
- OHTS: 1.4% of general population
  - More common in females, increased age
  - 6x more likely to have glaucoma
- Prevalence in patients with open angle glaucoma = 13.8%
  - POAG = 8%
  - OHT = 1.5%
  - NTG = 25%
- Pathogenesis, source unclear
  - More common in blood disorders, low platelets, nocturnal HTN



Hsia Y, et al. Graefe Arch Ophth Sept, 2019
Kwon J, et al. Glaucoma. Am J Ophthalmol. April 2017.

Drance Hemes in Glaucoma

- Negative prognostic sign
  - May indicate progression / damage
- Border at RNFLD and healthy retina
  - ST and IT – associated with most damage
- Normally disappears after 2-6 mos



84% from OHTS were missed in exam !

Healey, RP et al. Blue mountain eye stud, Ophth 1998.
DL Budenz, et al. Ophth 2006.

VF Loss in NTG…

- 1st - is it glaucoma-like loss ?
  - And then, is it *NTG-like* loss ?
- NTG defects…
  - closer to fixation and deeper
  - > progression compared to HTG
  - **Superior arcuate zone – may progress faster (note: relate to next slide)**

Ganeshrao SB et al. IOVS 2019

RNFL
NTG vs. HTG


Graefe's Archive for Clinical and Experimental Ophthalmology
July 2018, Volume 256, Issue 7, pp 1245–1256 | Cite as

Structural changes of macular inner retinal layers in early normal-tension and high-tension glaucoma by spectral-domain optical coherence tomography

Authors Authors and affiliations

Florian S. M. Edlinger, Laura M. Schrems-Hoesl, Christian Y. Mardin, Robert Laemmer, Friedrich E. Kruse,

- Macular vs. Peripapillary for discriminating normal vs. glaucoma
  - NTG w/o VF loss
  - NTG w/ VF loss
  - HTG w/o VF loss
  - HTG w/ VF loss

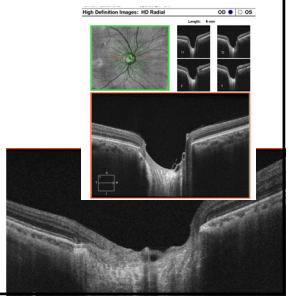
global pRNFL in all groups ***…except***

NTG pre-perimetric group
→ ***inferior pRNFL***

Enhanced Depth Imaging (EDI) on OCT

1. Posterior laminar displacement noted in glaucoma
   - Less so in NTG eyes
   - Not currently enough diagnostic accuracy

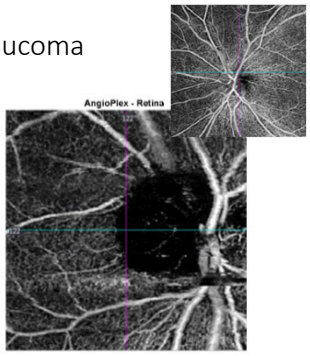
2. Choroidal thickening



Lee EJ, et al. PLOS One, April 2016.
Li L et al. Acta Ophth, 2016.

OCT-Angiography in Glaucoma

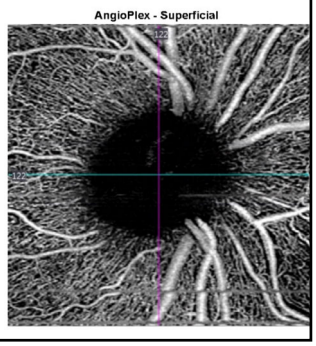
- Vessel Density (VD)
  - Parafoveal and *Circumpapillary* VD of value
  - Superficial and deep capillary plexus
- *Pre-perimetric* and *independent of structural loss*
- Corresponds to OPP



Yarmohammadi A, Ophth 2016
J Glaucoma 2018

OCT-A: Unique to NTG ?

- Especially important in NTG, given vascular significance
- Reduced retinal peripapillary capillary (RPC) vessel density (VD) adjacent to areas with history of drance heme



Xu H, et al. Graefe's 2018.