

Controversies and Consensus in Glaucoma

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Disclosure

- ▶ I have received support in the past from: Alcon, Allergan, Centervue, EyeiC, Glaukos, Merck, Oculus, Optovue, Reichert, Synemed

Controversial Topics

- ▶ What are the ocular risk factors for glaucoma?
- ▶ What are the systemic risk factors for glaucoma?
- ▶ What structural tests and findings are necessary to establish a diagnosis of glaucoma?
 - Photography?
 - OCT?
- ▶ Is OCT a valid means of diagnosing and monitoring glaucoma?
- ▶ What functional tests and findings are necessary to establish a diagnosis of glaucoma?
- ▶ What is the role of electrodiagnostics in the evaluation of glaucoma suspects?

Risk Factors (Ocular)

Intraocular Pressure (IOP)

- ▶ Although POAG may develop at any IOP, there is strong evidence supporting higher mean IOP during FU as a risk factor for development and progression of glaucomatous damage.
- ▶ There is insufficient evidence... to elucidate which IOP parameter (mean, peak and/or fluctuation,... etc.) is most important in determining risk...
- ▶ There is insufficient evidence implicating IOP fluctuations as an independent risk factor for glaucoma development or progression.

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Central Corneal Thickness (CCT)

- ▶ There is strong evidence supporting the role of CCT as an important predictive factor for OAG development in OHTN and glaucoma suspects. Baseline CCT measurements should be obtained in patients suspected of having glaucoma.
- ▶ Algorithms to correct IOP based on CCT are not recommended for routine use in clinical practice.
- ▶ There is insufficient evidence to conclude whether or not CCT is a true independent risk factor or whether its effect is related to a tonometric artifact.

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Corneal Hysteresis (CH)

- There is strong evidence implicating lower CH as a risk factor for glaucoma development and progression.
- There is insufficient evidence about the mechanisms by which CH is associated with the risk of glaucoma progression.

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The problem with CCT-based IOP adjustment



Thickness is NOT resistance

Ocular Response Analyzer Technology The instrument

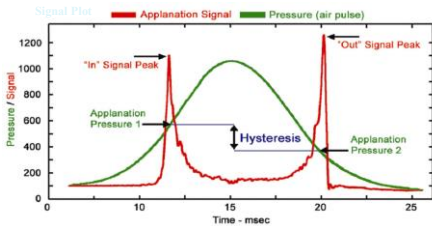
- 2002: Clinical research with ORA commences
- 2005: The 1st generation ORA was made commercially available
- 2012: Generation II ORA was launched
- 3rd Generation "ORA G3" Introduced September 2015

Measures:

- Corneal Hysteresis (CH)
- Goldmann-correlated IOP (IOP_G)
- Corneal compensated IOP (IOP_{CC})



Applanation Signal Plot



Corneal Hysteresis as a Risk Factor for Development of Glaucoma

- Prospective observational study
 - 287 eyes of 199 patients suspected of having glaucoma followed for an average of 3.9 ± 1.8 yrs.
 - VF normal at baseline
 - Progression = 3 consecutive abnormal VF's**
- 54/287 (19%) showed progression
- CH lower in those showing progression
 - 9.5 ± 1.5 mmHg in progressing
 - 10.2 ± 2.0 mmHg in non progressing $P=0.012$
 - Each 1mm lower CH means 22% greater risk progr.
 - Still predictive in multivariate analysis
 - After adjusting for age, IOP, CCT, PSD

Medeiros FA, Meira-Freitas D et al. *Ophthalmology* 2013;120(8):1533-1540.

Corneal Hysteresis and Progressive RNFL Loss in Glaucoma

- 186 eyes of 133 patients with OAG followed for an average of 3.8 ± 0.8 years
- Investigate the relationship between baseline CH, CCT, average IOP and rates of RNFL loss during follow up
- Each 1mmHg lower CH was associated with a 0.13 μ m per year faster rate of RNFL loss. ($P=0.015$)
- GAT IOP was also associated with a faster rate of RNFL loss ($P=0.010$)
- CCT, older age and AA ancestry were **not** associated with faster rate of RNFL loss

Zhang C, Tatham AJ, Abe RV, Diniz-Filho A, Zangwill LM, Weinreb RN, Medeiros FA. *AJO* (2016), doi: 10.1016/j.ajo.2016.02.034

Myopia

- ▶ Existing evidence suggests that individuals with myopia have an increased risk of developing OAG, with the risk being greater for people with high myopia.
- ▶ Diagnosis of glaucoma among myopic eyes can be challenging.
- ▶ Confirmed evidence of glaucomatous progression from a well-defined baseline is important for a correct diagnosis in many myopic individuals.

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Optic Disc Hemorrhage (ODH)

- ▶ Disc hemorrhage is associated with increased risk of developing and it is a marker for glaucomatous progression.
- ▶ Consideration of treatment escalation or closer follow-up should be given for patients presenting with ODH's.

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Disc Hemorrhages in OHTS

- ▶ Purpose:
 - To compare the rates of detection of ON hemorrhages by clinical examination and by review of ON photos
- ▶ Methods
 - 1618 patients underwent exam q 6 months
 - DFE every 12 months
 - Undilated exam on alternate visits
 - Stereo photos taken q 12 months
 - Mean FU: 8 years

Budenz DL, Anderson DR, et al Ophthalmology. 2006 Dec;113(12):2137-43

Results

- ▶ ON hems detected BEFORE POAG endpoint in 128 eyes of 123 participants
- ▶ 16% detected by both exam and photo review
- ▶ 84% detected by review of photos ALONE
- ▶ Risk factors for hem appearing:
 - Age, CCT, C/D, PSD, +FH, +smoking

Results

- ▶ Presence of ONH increased risk of POAG developing by 6-fold in univariate analysis
 - 3.7-fold in multivariate
- ▶ 8 year incidence of POAG:
 - Without disc hem: 5.2%
 - With disc hem: 13.6%
- ▶ Median time to development of POAG after hem appears
 - 13 months

Conclusions

- ▶ Stereo photos are more sensitive in detecting ON hemorrhages
 - Despite the fact that exams were performed twice as many times as photos!
- ▶ ONH increased the risk of developing POAG (600%)
- ▶ BUT, most eyes (86.7%) did NOT develop POAG with median FU time of 31 months after hem appeared

Rob's Analysis

- ▶ Take stereo photos!
- ▶ Review them carefully!
- ▶ If a ON hem appears, consider the patient to be at higher risk of developing POAG
 - But don't necessarily have to begin treatment
- ▶ Remember: OHTS was not evaluating NTG
 - ON hems routinely recognized as risk factor in NTG and POAG

Does blood supply matter in glaucoma?

The Evidence *Against* Blood Supply as a Risk Factor for *Development and/or Progression* of Glaucoma

Factors NOT Predictive

- ▶ Ocular Hypertension Treatment Study¹
 - Migraine
 - Cerebral vascular accident
 - High OR low blood pressure
 - Use of oral Beta blockers, Calcium channel blockers
 - Diabetes
- ▶ Early Manifest Glaucoma Trial²
 - High blood pressure
 - Cardiovascular disease
 - Migraine or Raynaud's Disease
 - Smoker (current or prior)

1. Kass M et al *Arch Ophthalmol*. 2002;120(6):714-720.
2. Leske MC et al *Oph Volume 114, Issue 11*. 2007, 1965-1972

Collaborative NTG Study No added risk

- ▶ Blood pressure
- ▶ Pulse rate
- ▶ Cardiac arrhythmia
- ▶ Major cardiovascular crisis
 - Hypotension
 - Shock
 - Blood transfusion
 - Major surgery

Risk Factors That Did *Not* Affect Risk of Progression

- ▶ Cardiovascular disease
 - HTN
 - Angina
 - Myocardial infarction
- ▶ Diabetes mellitus
- ▶ Peripheral vascular disease
- ▶ Raynaud phenomenon
- ▶ Anemia
- ▶ Tendency for low blood pressure
- ▶ Family history of DM and stroke

Risk factors for progression of VF abnormalities in NTG AJO. 2011; 131:699-708

Results

- ▶ “HTN, H/O major surgery, FH of Stroke or DM occurred in a substantial percentage of patients but failed to show up as factors influencing the rate of deterioration.”
- ▶ Migraine and disc hemorrhage were the only factors shown to affect the course of NTG
 - Are these factors evidence of too little blood flow or too much?? (vasodilation?)



Ocular Perfusion Pressure and Glaucoma

- ▶ $SPP = SBP - IOP$
- ▶ $DPP = DBP - IOP$
- ▶ $MPP = 2/3 \text{ mean arterial pressure} - IOP$
- ▶ $\text{Arterial Pressure} = DBP + 1/3(SBP - DBP)$

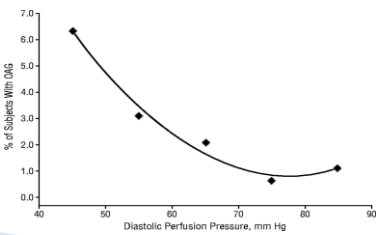


OPP and Glaucoma: Population Studies

- Baltimore Eye Survey
 - AA and Caucasian
- ▶ Egna-Numarkt Study
 - Caucasian
- ▶ Barbados Eye Study
 - African-Caribbean
- ▶ Proyecto Ver
 - Hispanic

Tielisch, Katz, Sommer, Quigley, Javitt. Arch Ophthalmol 1995;113:216-21
Bouillon-Buich, Marchini G, Marraffa M et al. Ophthalmology 2000;107:1287-93
Leske MC, Weinreb N, Nemesure B, et al. Arch Ophthalmol 2002;120:954-9 Quigley HA, West SK, Rodriguez J, et al. Arch Ophthalmol 2001;119:1819-26

OPP: Proyecto VER



Quigley HA, West SK, Rodriguez J, et al. Arch Ophthalmol. 2001;119:1819-26.



Ocular Perfusion Pressure (OPP)

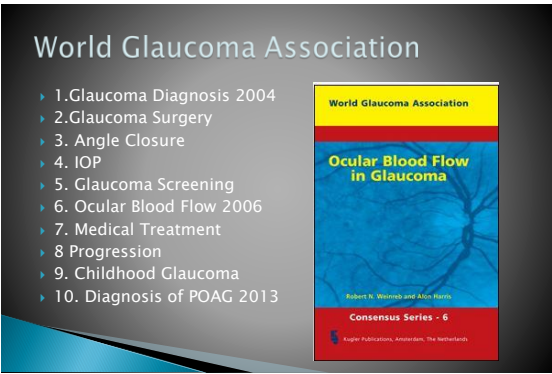
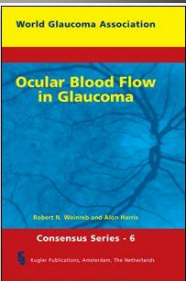
- ▶ Low OPP ...is associated with increased prevalence of OAG in cross-sectional studies.
- ▶ The value of OPP monitoring in daily clinical practice is not established.
- ▶ Due to the intrinsic relationship between OPP and IOP, it is difficult to establish an independent contribution of OPP as a risk factor for the development of OAG.

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World Glaucoma Association

- ▶ 1. Glaucoma Diagnosis 2004
- ▶ 2. Glaucoma Surgery
- ▶ 3. Angle Closure
- ▶ 4. IOP
- ▶ 5. Glaucoma Screening
- ▶ 6. Ocular Blood Flow 2006
- ▶ 7. Medical Treatment
- ▶ 8. Progression
- ▶ 9. Childhood Glaucoma
- ▶ 10. Diagnosis of POAG 2013



WGA Consensus on Blood Flow

- ▶ Ft. Lauderdale on May 2, 2009
- ▶ Goals:
 - To obtain consensus on the relationship between ocular blood flow and glaucoma
 - To establish a foundation for OBF research of glaucoma and the best practice for its testing in clinical practice.
- ▶ Consensus statements and comments based on published literature and expert opinion

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

WGA Consensus Points

- ▶ Low ocular perfusion pressure (OPP) (the difference between systemic blood pressure and intraocular pressure) is associated with increased prevalence of open-angle glaucoma in cross-sectional studies.
- ▶ *Comments:* The value of OPP monitoring in daily clinical practice is not established. Due to the intrinsic relationship between OPP and IOP, it is difficult to establish an independent contribution of OPP as a risk factor for the development of glaucoma.

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

The Question

- ▶ Do we have an accurate, valid means of measuring blood flow to the optic nerve?
 - That is clinically useful?

Consensus Points

- ▶ At the present time, there is no single method for measuring all aspects of ocular blood flow and its regulation in glaucoma.
- ▶ Low ocular perfusion pressure (OPP) (the difference between systemic blood pressure and intraocular pressure) is associated with increased prevalence of open-angle glaucoma in cross-sectional studies.
- ▶ *Comments:* The value of OPP monitoring in daily clinical practice is not established. Due to the intrinsic relationship between OPP and IOP, it is difficult to establish an independent contribution of OPP as a risk factor for the development of glaucoma.

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

Consensus Point

- ▶ Certain drugs, even when formulated in an eye drop, may have an impact on ocular blood flow and its regulation.
 - Comment: The impact of eye drop related changes in OBF on the development and progress of glaucoma is unknown.
 - Some data support increased blood flow and the enhancement of OBF regulation with CAI's. These appear to exceed what one would expect from their ocular hypotensive effect alone.

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

Consensus Points

- ▶ IOP is positively (but weakly) correlated with BP
 - For every 10mm change in SBP, there is a 0.5mm change in IOP
- ▶ Association between BP and the development of glaucoma is weak
- ▶ It is unclear whether the level of BP is a risk factor for having or progressing OAG in an individual patient.
- ▶ Lower OPP is a risk factor for primary OAG.
- ▶ OBF parameters measured with various methods are impaired in OAG, especially in NTG
- ▶ Vascular dysregulation may contribute to the pathogenesis of glaucoma, more likely in people with lower IOP.

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

Conclusion

- ▶ "The relationship among BP, IOP and development of OAG is complex and requires further investigation."

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

Take Home Points

- ▶ The role of blood supply as a risk factor in glaucoma is poorly understood and remains controversial
- ▶ Be aware of vascular health issues in our glaucoma patients
 - Low Blood pressure
 - Vascular dysregulation e.g. Migraines
- ▶ Measure BP and calculate OPP

Take Home Points

- ▶ Lower IOP improves OPP
- ▶ Higher systemic BP improves OPP but don't necessarily want to raise BP
 - Stroke #3 cause of death in US behind CVD and CA!
- ▶ Avoid drugs that lower systemic BP beyond patient's desired systemic control
- ▶ Avoid nocturnal hypotension
 - Use HTN meds in the AM in consultation with the patient's PCP/internist
- ▶ Encourage good lifestyle habits
 - Diet
 - Exercise
 - Stop smoking
 - Avoid headstands with yoga
- ▶ Refer for appropriate evaluation and management of possible risk factors
 - Sleep apnea
 - Vasospasm

For those who wish to drown

- ▶ Major Review Article: 24-hour Intraocular Pressure and Ocular Perfusion Pressure in Glaucoma
 - Quadrantal L, Katsanos A et al Surv Oph 58:26--41, 2013
- ▶ Blood Pressure, Perfusion Pressure, and Glaucoma
 - J Caprioli and A Coleman, on behalf of the blood flow in glaucoma discussion group
 - Am J Ophthalmol 2010;149:704-712.
- ▶ Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

Risk Calculators

- ▶ Predictive models (risk calculators) may provide objective assessment of individual risk and their use should be considered in patients suspected of having glaucoma.
- ▶ Current validated risk calculators apply only to OHTN patients. Moreover, they do not include all known risk factors.

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OHTS/EGPS 5-Year Risk Calculator

www.ohts.wustl.edu/risk/calculator

FACTORS							
?	Age	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
		1 st	2 nd	3 rd	1 st	2 nd	3 rd
?	Untreated Intraocular Pressure (mm Hg)	25	25	25	25	25	25
?	Central Corneal Thickness (microns)	555	555	555	555	555	555
?	Vertical Cup to Disc Ratio by Contour	0.50			0.50		
?	Pattern Standard Deviation						
?	Humphrey Octopus loss variance (dB)	2.0	2.0		2.0	2.0	

15.1% The patient's estimated 5-year risk (%) of developing glaucoma in at least one eye.

Gordon MO, Torri V et al; Ophthalmology. 2007;114(1):10-19.

Level of Risk Over 5 Years

- ▶ **Recommended Action**
- ▶ Low <5% Observe and Monitor
- ▶ Moderate 5% – 15% Consider Treatment
- ▶ High >15% Treat
- ▶ Adapted from Weinreb RN et al. *Am J Ophthalmol.* 2004;5

Risk Assessment: Systemic Factors

Age, Race

- ▶ POAG occurs at all ages, and the incidence and prevalence accelerates with age.
- ▶ Older age is a risk factor for glaucoma onset and progression.
- ▶ Populations with the highest incidence and prevalence of OAG have African ancestry.
 - Due to the earlier age of disease onset, the average duration of OAG may be greatest in individuals of African Ancestry.
- ▶ Hispanics may have higher incidence and prevalence of OAG than individuals of European ancestry (non-Hispanic whites).

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Ocular Hypertension Treatment Study

- ▶ Race did NOT increase risk of glaucoma development in the multi-variate analysis
- ▶ Blacks did have an 59% increase in risk in the univariate analysis but blacks had two other risk factors that DID increase risk in the multi-variate analysis
 - Larger vertical C/D ratio
 - Thinner central corneal thickness

Family History, Genetics

- ▶ First-degree relatives of POAG patients are at increased risk for glaucoma.
- ▶ Although studies have revealed there are multiple associated foci for OAG, there is little value for routine genetic testing to diagnose or predict the development of glaucoma at this time.

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Blood Pressure

- ▶ There is consistent, but weak, positive correlation between (diastolic and systolic) BP and IOP in population-based studies.
- ▶ Lower BP and OPP are associated with higher glaucoma prevalence and incidence across all racial groups.
- ▶ The relationships between DBP, SBP, systemic hypotension or systemic hypertension, and POAG are inconsistent.

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Blood Pressure

- ▶ The relationship between treatment of systemic hypertension and the development of POAG remains unclear.
 - There are data suggesting that some patients being treated for systemic HTN may be at greater risk for developing POAG.
- ▶ The role of nocturnal systemic hypotension in the development of glaucoma is unknown.

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Garway-Heath D et al. 2016 Klugler Publications

Review of literature and Consensus of experts

Blood pressure, perfusion pressure, and glaucoma

- ▶ Summaries of the pertinent literature and input from glaucoma researchers and specialists
- ▶ METHODS: Review and interpretation of selected literature and the results of a 1-day group discussion involving glaucoma researchers and specialists with expertise in epidemiology, blood flow measurements, and cardiovascular physiology.

Caprioli J, Coleman AL. Blood Flow in Glaucoma Discussion-A. IO 2010
May;149(5):704-12.

Results

- ▶ Accurate, reproducible, and clinically relevant measurements of blood flow within the optic nerve head and associated capillary beds are not fully achievable with current methodology.
- ▶ Autoregulation of blood flow in the retina and ONH occurs over a large range of IOP's and BP's.
- ▶ Regulation of choroidal blood flow is provided by a mix of neurohumoral and local mechanisms.
- ▶ Vascular factors may be important in a subgroup of patients with POAG, and particularly in patients with NTG and evidence of vasospasm.

Results (cont.)

- ▶ Low OPP and low BP are associated with an increased risk of glaucoma in population-based studies.
- ▶ The physiologic nocturnal dip in blood pressure is protective against systemic end-organ damage, but its effects on glaucoma are not well elaborated or understood.
- ▶ Large-scale longitudinal studies would be required to evaluate the risk of glaucomatous progression in non-dippers, dippers, and extreme nocturnal BP dippers.

Conclusions

- ▶ There is no evidence to support the value of increasing a patient's blood pressure as therapy for glaucoma.
- ▶ We lack crucial information about the microvascular beds in the optic nerve, and the appropriate methods to evaluate their blood flow.
- ▶ Cardiovascular safety concerns associated with increasing OPP and blood flow by increasing BP, especially in elderly patients.
- ▶ It is unlikely that safe and effective glaucoma treatments based on altering optic nerve perfusion will soon be available.

Sleep Apnea, Estrogen, Thyroid

- ▶ The evidence that obstructive sleep apnea is a risk factor for OAG is weak and warrants further study.
- ▶ There is insufficient evidence to determine if thyroid disease is associated with glaucoma.
- ▶ Although there is some evidence that reduction of estrogen production in post-menopausal women increase glaucoma risk, there is insufficient evidence for hormonal replacement
- ▶ Diabetes likely increases the risk for glaucoma onset.

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Meta-analysis of Association of OSA with Glaucoma

- ▶ Six studies with 2,288,701 participants
- ▶ Taiwan, USA, Turkey, France, China
- ▶ case-control studies
 - OR=2.46; 95% CI, 1.32-4.59, P=0.005
- ▶ cohort studies
 - OR=1.43; 95% CI, 1.21-1.69, P=0.000
- ▶ pooled OR for OSA patients who got:
 - CPAP treatment only
 - 1.13 (95% CI, 0.77-1.66, P=0.544),
 - who got any treatment
 - 1.17 (95% CI, 0.89-1.55, P=0.267),
 - No treatment
 - 1.22 (95% CI, 0.93-1.59, P=0.144).

Liu S et al J Glaucoma 2016;25:1-7)

Diabetes

- ▶ Diabetes likely increases the risk for glaucoma onset.¹
- ▶ OHTS:²
 - Initially found to be protective
 - Later: neither protective nor a risk factor
- ▶ European Glaucoma Prevention Study³
 - Also found no increase risk of glaucoma in diabetics

1. Diagnosis of POAG pp 161-187 Weinreb RN, Garway-Heath D et al. 2016 Klugler Publications
2. Gordon MO et al Arch Oph. 2002; 120: 714-720
3. EGPS Study Group Oph 2007 January; 114(1) 3-9

Structure

Optic Nerve Head Structure

- ▶ Clinical evaluation and documentation of the optic nerve head is essential for the diagnosis and the monitoring of glaucoma.
- ▶ Clinical diagnosis of glaucoma is predicated on the detection of a thinned RNFL and narrowed neuroretinal rim.
 - These features often appear first in the supero- or inferotemporal quadrants.

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Disc Rim, Nerve Fiber Layer (RNFL)

- ▶ Detecting progressive glaucomatous RNFL thinning and neuroretinal rim narrowing are the best currently available gold standards for glaucoma diagnosis.
 - Disease-related damaged should be differentiated from age-related change

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Visual Fields

- ▶ The diagnosis of glaucoma does not always require the detection of visual field defects with perimetry.
 - Perimetric defects that correspond to structural findings increase the likelihood of glaucoma.
 - Perimetry is indispensable for documentation and monitoring of functional decline in glaucoma.

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Neuroretinal Rim Tissue

- ▶ Assessment of the color and configuration (size and shape) of the neuroretinal rim is important to differentiate glaucomatous from non-glaucomatous optic neuropathies.
- ▶ A pale rim suggests non-glaucomatous optic neuropathy

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Cupping > Pallor: think glaucoma

Pallor > Cupping: Think something else

Wooldridge

Photography

- ▶ Photography is effective to document glaucomatous optic disc appearance and NFL damage
- ▶ Photography is particularly useful for detecting and documenting optic disc hemorrhage and rim color
- ▶ Stereo photography is particularly useful for detecting and documenting optic disc

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Imaging

- ▶ Imaging technologies including optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy (CSLO)(HRT) and scanning laser polarimetry (SLP) (GDx) provide an objective and quantitative approach to detect and monitor glaucoma.
- ▶ OCT may be the best currently available digital imaging instrument for detecting and tracking optic nerve structural damage in glaucoma.

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OCT

- ▶ RNFL is the most clinically useful parameter of the ones currently available with OCT.
- ▶ Macular RGC loss in glaucoma also can be detected by OCT.
- ▶ RNFL thickness and RGC loss are complementary

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Myopia

- ▶ It is difficult in myopic eyes to differentiate those with and without glaucoma.
- ▶ In myopic eyes, documented progressive optic neuropathy can be used to make the differential diagnosis of glaucoma.
- ▶ Reference data bases currently do not include highly myopic eyes and, therefore, are not appropriate for diagnosing RNFL damage in them.

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Vision Function

Visual Function

- ▶ Functional testing is essential for the evaluation, staging and monitoring of glaucoma.
 - Standard automated perimetry (SAP) is the reference standard for all functional testing.
- ▶ Clinical decisions should be made based on reliable VF tests.
 - VF defects should be reproducible and/or should be consistent with the location of the optic nerve defects.
 - The most important reliability index is the false positive rate.

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Visual Fields

- ▶ In the presence of glaucomatous optic neuropathy (GON), a glaucoma hemifield test (GHT) outside normal limits (ONL) in a reliable VF indicates that glaucomatous VF loss is present.
- ▶ When GON is suspected, a GHT criterion of ONL or borderline in a reliable VF increases the probability that an eye has glaucoma.

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Visual Fields

- ▶ Standard white-on-white Automated Perimetry (SAP) with a fixed testing matrix covering at least the central 24 degrees, is preferred for the diagnosis of glaucoma.
- ▶ Using the 10-2 strategy in addition to the 24-2 grid, can improve the detection of central functional loss.
- ▶ **Neither short-wavelength automated perimetry (SWAP) nor frequency doubling technology (FDT) have superior diagnostic precision to SAP.**

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Other Functional Tests?

- ▶ There is only weak evidence for the use of functional measurements other than SAP to detect the earliest signs of deterioration.
- ▶ There is a limited role for ERG testing in the routine diagnosis and management of glaucoma.
 - ***PERG and Photopic Negative Response (PhNR) are not substitutes for SAP or OCT imaging***

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Photopic Negative Response (PhNR)

- ▶ The PhNR in response to a brief flash is a negative-going wave following the b-wave of the cone electroretinogram (ERG) that is driven by retinal ganglion cells (RGCs). The function of RGCs is objectively evaluated by analyzing the PhNR. We reviewed articles regarding clinical use of the PhNR. The PhNR was well correlated with the visual sensitivity obtained by standard automated perimetry and morphometric parameters of the inner retina and optic nerve head in optic nerve and retinal diseases. Moreover, combining the PhNR with focal or multifocal ERG techniques enables the objective assessment of local function of RGCs. The PhNR is therefore likely to become established as an objective functional test for optic nerve and retinal diseases involving RGC injury.

Machida S. Journal of Ophthalmology
Volume 2012 (2012), Article ID 397178, 11 pages
<http://dx.doi.org/10.1155/2012/397178> accessed 3/18/18

Electrophysiology

- ▶ Studies are needed to elucidate the source and mechanism of reversible aspects of functional vision loss measured by PERG and PhNR testing
- ▶ Studies are needed to determine the extent to which PERG and PhNR signals depend on intact glial cell function in the retina and ONH
- ▶ Further Studies are needed to determine more precisely the positive and negative predictive value of PERG and PhNR testing for subsequent glaucoma progression and whether there is a value added to the current standard combination of VF and OCT.

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Which medication do I add next?

- ▶ Beta Blocker
 - Timolol
- ▶ Alpha Agonist
 - Alphagan
- ▶ Carbonic Anhydrase Inhibitor
 - Azopt/Trusopt
- ▶ Prostaglandin
 - Lumigan, Travatan, Xalatan, Zioptan
- ▶ Combination Agent?
 - Combigan, Cosopt, Simbrinza

Which medication do I add next?

- ▶ 1. Timolol
- ▶ 2. Alphagan
- ▶ 3. Azopt/Trusopt
- ▶ 4. Cosopt
- ▶ 5. Combigan
- ▶ 6. Simbrinza

IOP Response in primary use

- | | |
|--|------|
| ▶ Prostaglandins qd (pm) | –30% |
| ◦ Travatan, Xalatan, Lumigan | |
| ▶ Nonselective beta blockers qd (am) | –25% |
| ◦ Timoptic, Betimol, Betagan, Ocupress | |
| ▶ Betoptic-S bid (but safer) | –20% |
| ▶ Topical CAI's bid-tid | –20% |
| ◦ Azopt, Trusopt | |
| ▶ Alpha agonists bid-tid | –23% |
| ◦ Alphagan | |

A Panel Assessment of Glaucoma Management: Modification of Existing RAND-like Methodology for Consensus in Ophthalmology Part II: Results and Interpretation

KULDEV SINGH, BRIAN L. LEE, M. ROY WILSON, ON BEHALF OF THE GLAUCOMA MODIFIED RAND-LIKE METHODOLOGY GROUP

Singh K. et al. AJO 2008.

Adjunctive Therapy Agreements

- ▶ Adjunctive therapy is associated with diminished IOP response
- ▶ Adjunctive therapy should be limited to one drug from each class
- ▶ The panel agreed that adjunctive or switch therapy is indicated if
 - Monotherapy fails to achieve a target IOP
 - Therapy should be advanced whenever there is disease progression, regardless of IOP

Singh K, et al. AJO 2008. In press.

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Adjunctive Therapy Consensus

- ▶ Consensus *agreement* on the value of adding topical CAI's as adjunctive therapy to prostaglandins or beta blockers
- ▶ *Indeterminate* on the value of adding alpha agonists to prostaglandins or beta blockers
- ▶ *Disagreed* with initial use of combination agents

Singh K, et al. AJO 2008. 145; 3:575-581

Meta-analysis of the Efficacy and Safety of α_2 -Adrenergic Agonists, β -Adrenergic Antagonists, and Topical Carbonic Anhydrase Inhibitors With Prostaglandin Analogs

Angelo P. Tanna, MD; Alfred W. Rademaker, PhD; William C. Stewart, MD; Robert M. Feldman, MD

Objective: To perform a meta-analysis to estimate the intraocular pressure (IOP)-lowering efficacy and safety of α_2 -adrenergic agonists (AAs), β -adrenergic antagonists (BBs), and topical carbonic anhydrase inhibitors (TCAs) when used in combination with a prostaglandin analog (PGA).

Methods: MEDLINE, Embase, and the Cochrane Controlled Trials Register were systematically searched for relevant articles in April 2009. Ten observer-masked randomized clinical trials that reported baseline IOP while receiving PGA monotherapy and follow-up IOP while receiving combination therapy were identified. The pooled IOP-lowering efficacy achieved with each class of adjunctive agent was calculated using random-effects models. The frequencies of adverse events were pooled across studies and compared using Fisher exact test.

Results: Mean diurnal IOP reduction achieved in all 3

groups was statistically similar ($P=.22$). At trough, IOP reduction was greater in the TCAI ($P<.001$) and BB ($P<.001$) groups than in the AA group. Peak IOP reduction was similar in the 3 groups ($P=.66$). Eye or eyelid pain or burning and xerostomia were significantly more common in the AA group. Fatigue, weakness, or dizziness was more common in the AA and BB groups compared with the TCAI group. Taste disturbance was significantly more common in the TCAI group.

Conclusions: All 3 classes are similarly effective in lowering mean diurnal IOP when used in combination with PGAs. The AA class is statistically significantly less effective in reducing IOP at trough compared with BBs and TCAIs. The types of adverse events that were identified varied among the different classes of adjunctive therapies.

Arch Ophthalmol. 2010;128(7):825-833

Meta-analysis of Adjunctive Therapy

- ▶ **Conclusions:** All 3 classes are similarly effective in lowering mean diurnal IOP when used in combination with PGAs. The AA class is statistically significantly less effective in reducing IOP at trough compared with BBs and TCAIs. Fatigue, weakness, dizziness were more common with AA and BB groups. Taste disturbance more common in the TCAI group.

Tanna AP et al Arch Ophthalmol. 2010;128(7):825-833

Diurnal v. Nocturnal Effect of Medications

IOP is Higher at Night

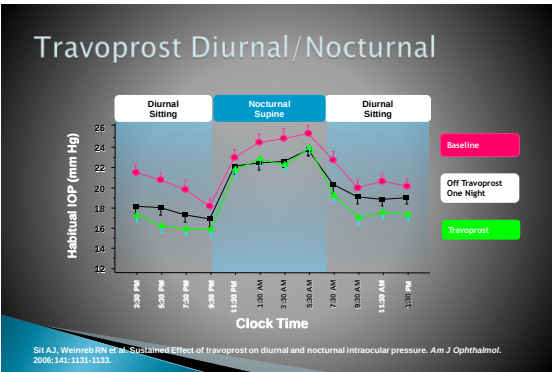
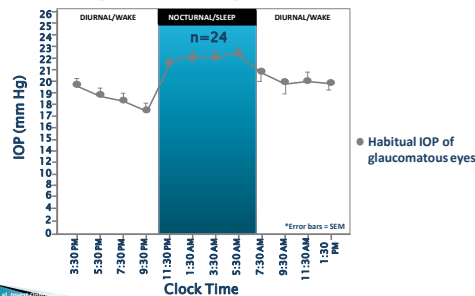
PURPOSE: To characterize the 24 hr pattern of IOP in untreated patients

METHODS:

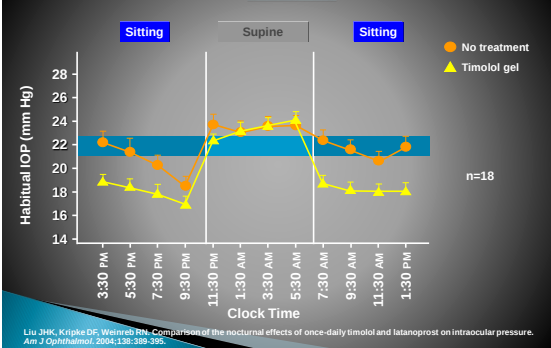
- ▶ 24 untreated patients with newly diagnosed glaucomatous optic discs and/or abnormal visual fields
- ▶ 24 hr IOP values obtained with a pneumotonometer at 2 hr intervals, in the sitting and supine position during the diurnal/wake period and in the supine position during the nocturnal/sleep period

Liu JH et al. Invest Ophthalmol Vis Sci. 2003; 44: 1586-1590.

IOP is Higher at Night



Nocturnal and Diurnal Habitual IOP

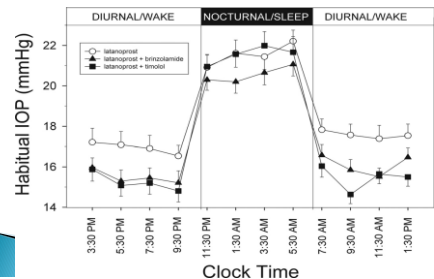


Comparing Diurnal and Nocturnal Effects of Brinzolamide and Timolol on IOP in Patients Receiving Latanoprost Monotherapy

- ▶ **Results:**
- ▶ Diurnal period, the mean IOP under brinzolamide or timolol add-on treatment was significantly lower than the baseline IOP in both the sitting and supine positions. There was no statistical difference between the 2 add-on treatments.
- ▶ Nocturnal period, the supine IOP under brinzolamide add-on treatment was significantly lower than both the baseline and the timolol add-on treatment.
- ▶ There was no difference in nocturnal IOP between the timolol add-on treatment and the baseline.

Liu J et al *Ophthalmology* 2009;116:449-454

Brinzolamide, Timolol added to Latanoprost



Diurnal and Nocturnal Effect of Latanoprost and Brinzolamide in NTG

- ▶ 44 eyes in 22 NTG patients
- ▶ IOP measured at 10AM,1PM,4PM,10PM,1AM,3AM
- ▶ Goldmann in sitting position
- ▶ Latanoprost as primary, Brinzolamide as adjunct
- ▶ Diurnal mean IOP reduction:
 - latanoprost and brinzolamide=19.8%, latanoprost=14.1%, P<0.001
- ▶ Nocturnal mean IOP reduction:
 - latanoprost and brinzolamide=13.4%, latanoprost=10.0%, P<0.05

Nakamoto K Yasuda N et al *J Glaucoma.* 2007 Jun-Jul;16(4):352-7.

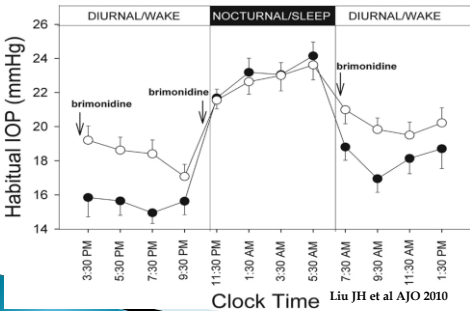
Diurnal and Nocturnal Effects of Brimonidine Monotherapy on Intraocular Pressure

John H. K. Liu, PhD, Felipe A. Medeiros, MD, PhD, J. Rigby Slight, MD, Robert N. Weinreb, MD

- 0.1% brimonidine TID for 4 weeks
- Results: The diurnal IOP mean was significantly lower than the baseline IOP in both the sitting and supine positions.
- No statistically significant change in IOP under the brimonidine treatment from the baseline during the nocturnal period.

Liu JH et al AJO 2010

Brimonidine Habitual Position



Medical vs. Laser Treatment

Which is the better first-line treatment?

SLT Considerations

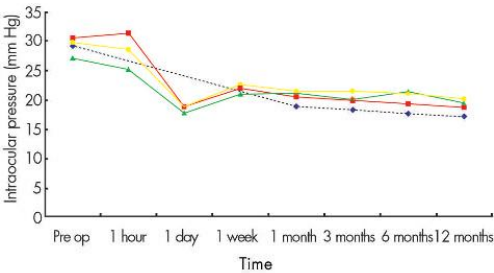
- Medical side effects
- Laser side effects
- Convenience/Compliance
- COST
 - Medicare only patients co-pay \$61.39
 - 98% of my private insurance have only their office visit co-pay after meeting their deductible.
- Duration of effect
- Diurnal effect

SLT v. latanoprost for the control of IOP in OHTN and OAG

- Prospective, randomized clinical trial 167 patients (167 eyes) with either OHT or OAG were randomized to receive SLT or latanoprost qhs
- Evaluated at 1 hour, 1 day, 1 week and 1, 3, 6, and 12 months.
- Success higher with latanoprost than with 90° and 180° SLT treatments
- SLT is an effective treatment
 - approximately 60% of eyes achieving an IOP reduction of 30% or more.

Nagar M Br J Ophthalmol 2005;89:1413-1417

IOP over time with treatment with latanoprost (blue diamonds), 90° SLT (green triangles), 180° SLT (yellow squares), and 360° SLT (red squares)



Selective Laser Trabeculoplasty as Primary Treatment for Open-angle Glaucoma A Prospective, Nonrandomized Pilot Study

- ▶ 45 eyes of 31 patients with OAG or OHT
 - (IOP 23 on 2 consecutive measurements) underwent SLT as primary treatment.
- ▶ IOP measured 1 hour, 1 day, 1 week, and 1, 3, 6, 12, 15, and 18 months postoperatively.
- ▶ During FU, patients were treated with glaucoma medications as required

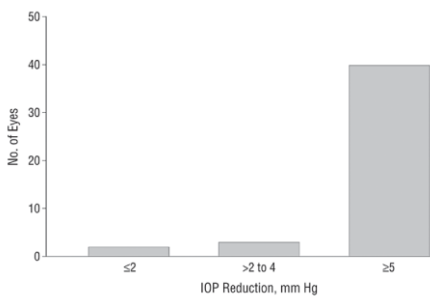
Melamed S et al Arch Ophthalmol. 2003;121:957-960.

Results

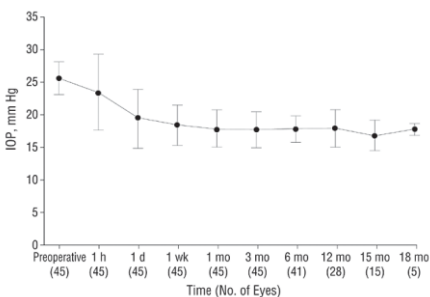
- ▶ An IOP reduction of at least 20% after SLT was defined as a successful treatment.
- ▶ Mean decrease in IOP: 7.7 ± 3.5 mm Hg (30%).
- ▶ Forty-three (95%) of 45 eyes treated had IOP reduction on 2 consecutive visits (± 2 mm Hg).
- ▶ When successful, the IOP reduction was sustained after SLT

Melamed S et al Arch Ophthalmol. 2003;121:957-960.

IOP Reduction (mm Hg)



POST SLT IOP Sustained



Results and Conclusion

- ▶ Only 2 eyes (4%) did not respond to SLT
- ▶ 3 eyes (7%) required topical medications to control their IOP at the end of the follow-up period.
- ▶ Forty eyes (89%) had a decrease of 5 mm or more.
- ▶ **Conclusion** SLT is effective and safe as a primary treatment for patients with OHT and OAG.

Melamed S et al Arch Ophthalmol. 2003;121:957-960.

Effect of Laser Trabeculoplasty on Nocturnal Intraocular Pressure in Medically Treated Glaucoma Patients

Alexander C. Lee, MD,¹ Sameh Mosaed, MD,¹ Robert N. Weinreb, MD,¹ Daniel F. Krieger, MD,² John H. K. Liu, PhD¹

Purpose: To evaluate the effects of laser trabeculoplasty on 24-hour intraocular pressure (IOP) in a group of medically treated open-angle glaucoma patients.

Design: Prospective experimental study.

Participants: Eighteen open-angle glaucoma patients.

Methods: Laser trabeculoplasty (180°) was performed on 28 eyes of 18 glaucoma patients. Twenty-four-hour IOP data were collected in a sleep laboratory before and 45 to 80 days after the procedure. Measurements of sitting and supine IOP were taken during the 16-hour diurnal/wake period, and measurements of supine IOP were taken during the 8-hour nocturnal/sleep period in 2-hour intervals.

Main Outcome Measures: Changes in the mean, peak, and range of IOP during the office-hour, diurnal, nocturnal, and 24-hour periods.

Results: Compared with the baselines, changes in the mean, peak, and range of IOP were not significant during the office-hour period and during the diurnal period in either the sitting or the supine position. The mean, peak, and range of IOP were reduced significantly during the nocturnal period in the supine position. Mean and peak 24-hour IOP were reduced significantly in the habitual body positions (sitting during the diurnal period and supine during the nocturnal period). The reduction of mean 24-hour IOP in the supine position also was significant.

Conclusions: In this group of medically treated open-angle glaucoma patients, laser trabeculoplasty reduced IOP more consistently during the nocturnal period than during the diurnal period. *Ophthalmology* 2007; 114:666-670 © 2007 by the American Academy of Ophthalmology.

Comparison of fluctuations of IOP before and after SLT in NTG patients

- ▶ Ten patients with NTG
- ▶ Habitual IOP measured before and after SLT
- ▶ IOP fluctuation measured with Sensimed Triggerfish
- ▶ Mean 24 hr. IOP
 - Pre-SLT: 13.5 ± 2.5 mm
 - Post SLT: 11.3 ± 2.4 mm at 3 months
- ▶ Diurnal IOP fluctuation not significantly reduced
- ▶ Nocturnal fluctuation was significantly reduced
 - 290 ± 86 mVEq before SLT to 199 ± 31 mVEq post SLT



Tojo N, Oka M, Miyakoshi A, et al. J Glaucoma. 2013; Nov
16. [Epub ahead of print].