Ocular Blood Flow and glaucoma?
State of the science 2009

“At the present time, no single blood flow imaging device is capable of evaluating ocular blood flow relevant to glaucoma.

“A comprehensive approach, utilizing multiple imaging technologies is required for meaningful insight into the multiple vascular beds of the eye.”

Consensus statement of the WGA 2009

POAG is a progressive, chronic optic neuropathy in adults in which intraocular pressure (IOP) and other currently unknown factors contribute to damage and in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an anterior chamber angle that is open by gonioscopic appearance.

—ala AAO PPP

“Can glaucomatous optic neuropathy be induced by a primary non-IOP-related insult . . . alone??” —Claude Burgoyne

Seriously . . .

David Sackett, MD [1934-2015]

• Widely regarded as the father of evidence-based medicine.

Half of what you’ll learn during training will be shown to be either dead wrong or out-of-date within 5 years . . .

...the trouble is that nobody can tell you which half.

Disclosures: Speakers' Bureau / Consultant - Alcon, Allergan, Regeneron
Stockholder: HPO
Blood pressure and glaucoma
V P Gusa, E S Acker, A Harris

ABSTRACT
Although intracranial pressure (ICP) is considered a relevant risk factor for the development of glaucoma, and the IOP parameter is subject to treatment, there is insufficient evidence to suggest that glaucoma may continue to progress despite lowering ICP to target levels. Several authors have implicated vascular risk factors in the pathogenesis of glaucoma. Among these, the role of arterial hypertension remains of particular interest.

The aim of the present study was to investigate the relationship between IOP and MAP and the potential risk of glaucoma.

Methods:
A retrospective analysis of IOP and blood pressure measurements obtained from 100 patients diagnosed with glaucoma and 100 age-matched healthy controls was conducted. The mean arterial pressure (MAP) was calculated from the systolic and diastolic blood pressure (BP) values using the formula MAP = (SBP + DBP)/3.

Results:
A significant correlation was found between IOP and MAP in both the glaucoma and control groups. The mean IOP was significantly higher in the glaucoma group compared to the control group (p < 0.05).

Conclusion:
Our findings suggest that arterial hypertension may contribute to the pathogenesis of glaucoma. Further studies are needed to investigate the role of arterial hypertension in the development and progression of glaucoma.
Optical Coherence Tomography Angiography of Optic Disc Perfusion in Glaucoma

Yuli Ju, MD, PhD; Pei Wu, MD; Weiping Wang, MD; Tiejie Zhang, PhD; John C. Morrison, MD; Jihua Su, MD, PhD; Lin H. Lambrick, MD; Donna M. Gault, MD; Jennifer K. Tinson, MD; Robert Edwards, MD; Warren F. Krowis, MD; James P. Popper, MD; Daniel Hwang, MD, PhD

Purpose: To compare optic disc perfusion between normal subjects and subjects with glaucoma using optical coherence tomography (OCT) angiography, and to detect optic disc perfusion changes in glaucoma.

Design: Observational, prospective study.

Methods: Twenty-four normal subjects and 11 patients with glaucoma were included. OCT angiograms were obtained using high-speed 1050-nm, wavelength-scanning source OCT instrument. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to compute 3-dimensional optic disc angiograms. A disc flow index was calculated from 4-registered volumes. Correlation scanning near-infrared microscopy (CSNM) was used to measure disc perfusion areas. The flow index was calculated as the ratio of perfused disc area to total disc area. Multiple linear regression analysis, logistic regression analysis, and receiver operating characteristics were used to analyze the correlation. The area under the curve (AUC) was compared by the Wilcoxon rank sum test. Significant differences were considered if AUC was >0.9.

Results: In normal subjects, a dense microvascular network was visible on OCT angiography. The network was rarely attenuated in subjects with glaucoma. The intra- and inter-reader variability, interobserver repeatability, and normal population variability of the optic disc flow index were 1.9%, 4.2%, and 5.0% CV, respectively. The disc flow index was reduced by 25% in the glaucoma group (P = 0.003). Sensitivity and specificity were both 90% using an optimized cutoff. The flow index was highly correlated with IOP (r² = 0.725, P = 0.001). The correlations were significant even after accounting for age, ODI area ratio, NLI, and rim area.

Conclusions: Optical coherence tomography angiography, generated by the new SSADA, repeatable measures optic disc perfusion and may be useful in the evaluation of glaucoma and glaucoma progression. Ophthalmology 2014;121:1730-1732. © 2014 by the American Academy of Ophthalmology.
Generalized and local effects.

Maybe this helps explain the asymmetry that is so prevalent in glaucoma. Think: "VF, rim tissue, PPA . . . .
And just late last year...

- A study from a registry in England suggested an association between glaucoma* and vascular dementia* but not between glaucoma and Alzheimer disease*.

[*Alzheimer and vascular dementia are both neurodegenerative diseases and glaucoma is now being lumped into that bucket, too.]

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**Ocular Perfusion Pressure & Glaucoma Progression – emerging paradigms**

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**Optic Nerve HEAD anatomy – blood flow considerations**

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**Structural evaluation - Diagnosis enhanced depth imaging [choroid]**

- Choroidal thickness and perfusion/flow evaluation
- Age, axial length, CCT, and diastolic ocular perfusion pressure are significantly associated with choroidal thickness in glaucoma suspects and glaucoma patients.
- Degree of glaucoma damage was not consistently associated with choroidal thickness.

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**Hey! Maybe its choroidal blood flow**

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**DX: POAG, ??? Is there a blood-flow problem here???**
Choroidal blood flow (arbitrary units)

Note: increased IOP induces
- posterior rotation of the peripapillary sclera
- flattening of the cup floor
- thinning of the lamina cribrosa and the prepapillary neural tissue and
- anterior movement of the central optic nerve relative to the LC

Which may be complementary to reduced blood flow OR a result of same

Glaucomatous damage cascade

1. IOP compromises perfusion pressure
2. Resulting in ischemia at ONH
3. Growth factors from LGN fail to reach ganglion cells
4. Cell bodies, lacking growth factors, initiate apoptosis
5. Cell death by apoptosis
6. Glutamate release from ganglion cells
7. Death of adjacent axons in bundle from neurotoxicity from amino acids such as glutamate and NMDA (N-methyl D-aspartate). (Zombies)

Distribution of IOP in a general population.

Primary Open-Angle Glaucoma

Conclusions: Patients with POAG or NTG exhibit similar alterations in ocular and systemic circulation in the early stages of their disease process. This finding highlights the importance of considering vascular risk factors in both conditions and raises questions about the current separation of the two conditions into distinct clinical entities.

Perfusion Pressure is a Result of a Delicate Balance Between IOP and Blood Pressure

Lower Perfusion Pressure Is Associated with Increased Risk for Open Angle Glaucoma


mean perfusion pressure = \( \frac{2}{3} \) (mean arterial pressure - IOP)

Where mean arterial pressure = diastolic BP + 1/3 (systolic BP – diastolic BP)
Emerging importance of diastolic BP

- Low mean diastolic BP is consistently associated with structural glaucoma progression (Rim tissue, RNFL)


*Significantly lower diastolic perfusion pressure was observed in those taking oral hypotensive medications (as in beta-blockers)
Conclusions and future directions
One of the reasons why our understanding of the relation between OPP and glaucoma is still limited lies in the difficulties to measure retinal and ONH BF [55-58]. Doppler optical coherence tomography may become a technique capable of measuring BF in a valid and reproducible way [24-26]. This improvement in technology is associated with the hope of gaining more insight into ocular BF regulation.
Conclusions and guidance

• In conclusion, the magnitude and duration of nocturnal hypotension identify patients with NTG who have VF progression.

• Ambulatory monitoring of systemic BP should become part of routine assessment of patients with NTG, particularly among those who continue to progress despite IOP lowering.

Conclusions and guidance

• Nocturnal BP should be considered a modifiable risk factor in NTG.

• Randomized trials will be required to assess the efficacy of different interventions designed to avoid nocturnal hypotension to prevent VF loss in patients with NTG, as well as to test the effect of more aggressive IOP-lowering therapy in these cases.

Conclusions and Guidance

• Blood flow measurements could guide changes in treatment protocol with emphasis on normalization of circulatory alteration rather than just IOP.

Reduced perfusion - More Risk factors

• Autoregulation disturbances
• Vasospastic Disorder
• Migraine
• Increased resistance

• Reduced blood flow (20 low BP) → Nocturnal hypoperfusion

• Sleep apnea syndrome

SAS and Normal Tension Glaucoma

• 50 sleep apnea patients were compared with 40 normals
• Prevalence of NTG among SAS pts was 5.9% (and 0% among the controls)
• Severity of SAS was correlated positively with [structural and functional elements]
  - IOP
  - MD
  - C/D
  - mean NFL thickness (HRTII)

SAS – Glaucoma connection  
(additional evidence)

- The prevalence of glaucoma in patients with obstructive sleep apnea is an estimated 27%!


Ocular blood flow and Obstructive Sleep Apnea Syndrome (OSAS)

- 31 patients with proven OSAS / 25 controls
- 12.4% of OSAS and none of the controls were diagnosed with glaucoma
- No differences in retinal circulation measures or IOP (implying IOP-independent risks)
- Positive correlation between MD and LV & retinal circulatory measures


SAS – Glaucoma connection  
(further evidence)

- In patients with OSAS, a high prevalence of glaucoma was found.
- Visual field defects may be due to optic nerve perfusion defects and these field defects also increase as the RI (resistance index) increases.


And, more recently raised questions... 

- Should OSAHS be included in the DDx of glaucoma?
- Is OSAHS another glaucoma or a contributor?
- Does lowering IOP in OSAHS arrest the progression of optic neuropathy?


“Fair and balanced”

- Found that there IS a relationship between IIH and AION and those using a C-PAP but not between glaucoma and C-PAP use.

Obstructive Sleep Apnea and Increased Risk of Glaucoma

A Population-Based Matched-Cohort Study

Cheng-Chung Lin, MA,1,2 Chen-Chen Hu, MD,1,2,3 Jun-Jie Ma, MD,1,2,3 Hong-Wei Chao, MD,1,2

Purpose: Previous studies have reported an increased prevalence of glaucoma in patients with obstructive sleep apnea (OSA). However, the risk of developing glaucoma (DAG) among patients with OSA remains unclear. The aim of the current study was to determine the incidence and risk factors for DAG among patients with and without OSA. Additionally, we sought to identify the prevalence of OSA among patients with DAG.

Patients and Methods: The study was based on data derived from the Longitudinal Health Insurance Database of 2011, which is a large insurance database in Taiwan. The study included 1,000 subjects with OSA and 1,000 subjects without OSA matched for age, gender, and comorbidities. The incidence of DAG was calculated using the Kaplan-Meier method. The hazard ratio (HR) for DAG was estimated using Cox proportional hazards regression. The significance level was set at 0.05.

Results: During the 5-year follow-up period, the incidence rate for DAG was 1.59 per 1,000 person-years in the OSA group and 1.00 per 1,000 person-years in the control group. The HR for DAG in the OSA group was 1.67 (95% CI: 1.17-2.36). After adjusting for age, gender, and comorbidities, the HR for DAG in the OSA group remained significant (HR: 1.56, 95% CI: 1.07-2.27).

Conclusions: Our results suggest that OSA is associated with an increased risk of subsequent DAG diagnosis during the follow-up period. The increased risk of DAG among patients with OSA is not only due to the presence of comorbidities but also due to the increased risk of DAG in patients with OSA. Further studies are needed to confirm these findings and to determine whether interventions to reduce the risk of DAG in patients with OSA are effective.
Conclusions about the role of translaminar pressure in glaucoma

In conclusion, CSF pressure as translaminar counter pressure against IOP seems to be of major importance in glaucoma, and future investigations are needed to elucidate the involvement of CSF pressure and its fluctuations in the development, progression and management of glaucoma.

Up to the present time, research in glaucoma was limited due to invasive ICP measurement methods.

Conclusions about the role of translaminar pressure in glaucoma

The role of the two-depth transcranial Doppler based non-invasive technology for measuring absolute ICP in glaucoma patients would be innovative and may provide an important aspect currently missing information in glaucoma pathology assessment and even change our whole understanding about glaucoma.

Importantly, to date, this non-invasive absolute ICP measurement method is the only available method that does not need an individual patient-specific calibration.

Breaking News

Paraphrasing the conclusions of the authors, considering ONLY CSFP and IOP without considering lamina cribrosa properties, orbital tissue, pia matter and subarachnoid space properties is unlikely to adequately characterize pathological processes in diseases like glaucoma and idiopathic intracranial hypertension.


How should glaucoma be managed comprehensively?

• **First**, lower IOP
  - Topical treatments? (betaxolol, brimonidine, brinzolamide, Gingko Biloba)
  - Exercise, weight loss
  - Lower cholesterol, blood sugar levels
  - Treat underlying vascular disorders (HT, SAS, CVD)
  - Etc.

• **Third**, reduce oxidative stress (Ca²⁺ blockade [BUT, not systemic β-blockers], supplements)

• **Second**, consider increasing perfusion (may be a consequence of lowered IOP)
  - Topical treatments? (betaxolol, brimonidine, brinzolamide, Gingko Biloba)
  - Exercise, weight loss
  - Lower cholesterol, blood sugar levels
  - Treat underlying vascular disorders (HT, SAS, CVD)
  - Etc.
NON-SELECTIVE Beta-blockers: 
Significant additional precaution

Topical β-blockers administered at night to those taking systemic β-blockers may reduce perfusion to the ONH plus β-blocker therapy to reduce IOP is ineffective at night.

Which brings us to . . .


Relationship between Nocturnal Hypotension and OPP (ocular perfusion pressure)

- Low BP at night, coupled with high IOP in supine position, compromise OPP
- Use systemic BP meds in the AM to minimize nocturnal hypotension
- Use IOP lowering drugs that lower IOP during the diurnal and nocturnal period
- Avoid IOP meds that lower systemic BP at night (beta blockers, alpha agonists)


Summary: OPP & 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 needed to take advantage of this modifiable risk factor


Let’s look at some practical aspects of IOP control / blood flow . . .

- PGAs
- Additivity
- Efficacy of β-blockers
- Efficacy of α-agonists
- Continuous IOP control

Let’s look at some practical aspects of IOP control . . .

Brimonidine 24-hr

Profiles of 24-hour IOP in the habitual body positions. Measurements were taken from 15 subjects sitting during the diurnal period and supine during the nocturnal period.

Open circles represent the baseline
Solid circles represent the brimonidine treatment.
Error bars represent standard error of the mean.
IOP = intraocular pressure.

Bottom line: brimonidine does not work at night

Conclusions: In subjects with OHT, brimonidine treatment for 6 weeks significantly reduces seated IOP during the day by increasing uveoscleral outflow. The lack of IOP effect at night can be explained by failure to overcome a normal nighttime reduction of uveoscleral outflow.
The holy grail of glaucoma whether it is diagnosis or management is . . .

CONTINUOUS IOP MEASUREMENT

Continuous IOP monitoring with a wireless ocular telemetry sensor: initial clinical experience in patients with OAG.


• Results from 15 patients (single 24-hour monitoring period)
  – Peaks (>1 hr) observed in 12/15 (80%) of patients
  – Management was changed in 11/15 (73%) based on the data!

53 yo treated glaucoma patient (PGA qhs + timolol/ICA comb); excellent reproducibility for two overnights: blue & yellow.


52 yo Asian female glaucoma suspect (PGA qhs Rx’d but may have been noncompliant); good reproducibility pattern for two overnights: blue & yellow.

Example

Moderate reproducibility in a 59 GS for two overnights blue & yellow.

Example

Poor reproducibility in a 20 GS for two overnights with spikes (n.b., pt has poor sleep habits). [app on your iPhone]

And one recent comment

There is no good evidence to suggest that IOP variability is an appropriate substitute for measuring true diurnal IOP (i.e., 24-hour fluctuation).

Paraphrased from:

What happens to glaucoma patients during sleep?

2013,

**KEY POINTS**

- Peak intraocular pressure, which has been found to be the best predictor of glaucomatous visual field progression, most likely occurs at night.
- Nocturnal intraocular pressure is dependent on the body position and may be significantly lowered in a 30° head-up position during sleep.
- A decrease or fluctuation in nocturnal ocular perfusion pressure increases the risk of glaucomatous visual field progression.
- The relationship between obstructive sleep apnea and glaucoma remains unclear, with smaller prospective studies reporting a positive association and longer retrospective cohort studies declining.

Closing thoughts

- How can IOP be monitored continuously?
- What impact may this have on management?
Schematic of implantable continuous IOP monitoring device

And more recently

• An Implantable Intraocular Pressure Transducer
  Implanted at cataract surgery

• An Implantable Intraocular Pressure Transducer

>/>= 3 measurements (each device)

Thank You,
Idaho Optometric Physicians