Disclosure

- I have received support from the following companies:
  - Alcon, Allergan, Biotissue, Centervue, EyeiC, Oculus,
  - Optovue, Synemed,

Ocular Blood Flow in Glaucoma
Robert P. Wooldridge, OD, FAAO

Larry 1999
- 46 yo WM referred as glaucoma suspect
- MH: no illnesses  FH: mother has glaucoma
- VA 20/15 OU
- IOP R 42  L 46
- SLE normal OU
- ON, VF as seen

2004

1999–2006
- IOP running 15–17 OU on Xalatan, after SLT OU
- VF, nerves stable
- 9/06/06
  - IOP R 16  L 17

2/10/1999
Larry 2009

- IOP running R 12–17 L 13–14
- On Xalatan and Combigan
- VF getting worse OD
- Now what?

Other Health Issues?

- No sleep apnea
- No migraines
- What else should we check??
- BP
- June 29: 102/56 P 48
- July 30: 121/74 P 51
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)

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

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?)

Footnotes:


Image references:

- Ocular Hypertension Treatment Study
- Early Manifest Glaucoma Trial
- Collaborative NTG Study
- Risk Factors That Did Not Affect Risk of Progression
- Results
The Evidence For Blood Supply as a Risk Factor for Development of Glaucoma

- Same cohort study of African-Caribbeans residing in Barbados, West Indies
- 9-year risk of developing glaucoma increased at lower
  - SPP (RR 2.0, CI 1.1–3.5)
  - DPP (RR 2.1, CI 1.2–3.9)
  - MPP (RR 2.6, CI 1.4–4.6)


Does Blood Pressure Matter?

- Circadian BP

Nocturnal Hypotension: Role in Glaucoma Progression

- 24 hour BP recording
  - NTG 38 patients; POAG 46; Controls 11
  - Means of the SBP, DBP, mean arterial pressure, and pulse pressure for 24 hours determined
  - The % nocturnal dip was calculated.
  - Masked assessment of VF for progression or stability was done on those 70 patients who had numerous fields plotted for more than 5 years.

Graham Drance et al Survey Ophh; 1999: 43, S10-S16

Results

- Patients with greater nocturnal BP dips were more likely to have shown field change, despite good IOP control.
- Patients who had field progression showed significantly lower nocturnal BP variables, with the dips of the SBP, DBP and mean arterial pressure significantly larger (systolic dip, P = 0.01)
- They also had a greater history of disc hemorrhages.

World Glaucoma Association

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

Page 4
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 NTC
- Vascular dysregulation may contribute to the pathogenesis of glaucoma, more likely in people with lower IOP.

Conclusion

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

Ocular Perfusion Pressure and Glaucoma

- SPP = SBP – IOP
- DPP = DBP – IOP
- MPP = 2/3 mean arterial pressure – IOP
- Arterial Pressure = DBP + 1/3(SBP – DBP)

OPP and Glaucoma: Population Studies

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

OPP Questions

- What is the normal circadian rhythm of OPP?
- How does OPP vary with sitting vs supine position?
- Does OPP change with age?
- Does the diurnal-to-nocturnal change in OPP differ by age group?
OPP Circadian Rhythm

- OPP was found to be higher in the older group than in the younger group throughout the 24 hours.
- The peak OPP was in the nocturnal period for both groups. (habitual position)
- Within each subject group, the average nocturnal OPP in the supine position was higher than the average diurnal OPP in the sitting position.
- The diurnal-to-nocturnal increase of OPP was larger in the older group than in the younger group.

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.


WGA Consensus Points

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The Question

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

At the present time, there is no single method for measuring all aspects of ocular blood flow and its regulation in glaucoma.

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Annette

- 69yoWF referred with large cups
- IOP
  - R 16, 11, 14 mmHg
  - L 18, 13, 16 mmHg
  - (three separate exams)
- DRA IOP R 15.3 L 17.5 CH R 9.8 L 9.9
- CCT R 599 L 603

That was Then
This is Now
OCTA in Glaucoma
Used Optovue Avanti OCT

Compared NFL thickness and VD in healthy, glaucoma suspect, and glaucoma patients in 261 eyes

Vessel Density: % of area occupied by flowing blood vessels in the area
circumpapillary region (cpVD) (750–mm wide annulus around the disc)
whole-image vessel density (wiVD) (entire 4.5×4.5-mm scan field)

Areas under the receiver operating characteristic curves (AUROC) were used to evaluate diagnostic accuracy

For differentiating between healthy and healthy eyes, the age-adjusted AUROC was highest for wiVD (0.94), followed by RNFL thickness (0.92) and cpVD (0.83).
The AUROCs for differentiating between healthy and glaucoma suspect eyes were highest for wiVD (0.70), followed by cpVD (0.65) and RNFL thickness (0.65).


153 eyes: 31 healthy eyes, 48 suspects, and 74 OAG pts.

VD higher in NL eyes followed by OAG suspects, mild OAG, and moderate to severe OAG eyes for wiVD (55.5%, 51.3%, 48.3%, and 41.7%, respectively) and for cpVD (62.8%, 61.0%, 57.5%, 49.6%, respectively) (P < 0.001 for both)

Conclusions: Decreased VD was significantly associated with the severity of VF damage independent of the structural loss. OCTA is a promising technology in glaucoma management, potentially enhancing the understanding of the role of vasculature in the pathophysiology of the disease

Yarmohammadi A Zangwill LM et al Oph 2016;123:2448-2448

In eyes with similar severity of OAG, cpVD was significantly lower in eyes with focal lamina cribosa (LC) defects than in eyes without an LC defect.

Reduction of vessel density was spatially correlated with the location of the LC defects

Factors associated with vessel dropout:

focal LC defects, more advanced glaucoma, reduced RNFL vessel density, thinner choroidal thickness, and lower diastolic blood pressure

Cause or effect TBD

Nocturnal Effect of Glaucoma Meds on IOP

- Timolol\textsuperscript{1,2} and brimonidine\textsuperscript{2} do NOT lower nocturnal IOP
- PGA’s\textsuperscript{1,3}, CAI’s\textsuperscript{4} DO lower nocturnal IOP
- Studies were not powered to determine if OPP was affected by medications in these studies (except ref #6)
- Timolol lowers BP and slows heart rate at night\textsuperscript{5}

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Do Topical Beta Blockers have an Effect on Night time BP?

- 275 patients
  - 161 with glaucoma: 131 NTG, 30 OAG
  - 114 with NAION
- Monitored 24-Hr IOP and BP
- 114 using topical BB BID (76 with NTG, 26 with POAG, and 12 with AION).

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Results

- Patients using topical beta blockers had:
  - Lower minimum nocturnal heart rate
  - Lower minimum nocturnal DBP
  - Greater percentage drop in nocturnal DBP
- More progression in VF loss
- Conclusion: The use of BB eyedrops, by aggravating nocturnal arterial hypotension and reducing the heart rate, may be a potential risk factor in susceptible individuals.

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OPP and Glaucoma Medications

- Cross over study of effect of different classes of IOP lowering meds on DPP
  - PCA and CAI significantly increased DPP at all time points
  - Beta-blocker significantly increased DPP from 4AM to 4PM but had no effect at other times
  - Alpha agonist significantly reduced DPP at multiple time points, primarily due to significant decrease in systemic BP
Effects of Bimatoprost and Timolol on Circadian IOP, BP and OPP

- OHTN or OAG patients treated with bimatoprost QD or timolol 0.5% bid.
- Measured IOP, BP, HR, OPP after 8 weeks.
- Mean 24h IOP was significantly lower with bimatoprost than timolol (15.7 vs 16.8 mmHg, p = 0.0003).
- Mean IOP during the day was significantly reduced from baseline by both drugs while mean IOP during the night was reduced by ~3 mmHg by bimatoprost and by ~1.1 mmHg by timolol.
- Timolol 0.5% significantly reduced the mean 24h systolic BP from baseline, the diastolic BP during the day hours, the HR during the night hours, and the mean 24h systolic OPP.


- Both Bimatoprost and Timolol 0.5% are effective in reducing the mean 24h IOP from an untreated baseline but Bimatoprost is more effective than timolol throughout the 24h.
- Timolol effect on IOP is reduced during the night hours and is associated with reduced BP, HR and ocular perfusion pressure.

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.

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.

Review of literature and Consensus of experts

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.

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 eg Migraines
- Measure BP and calculate OPP

For those who wish to drown

- Major Review Article: 24–hour Intraocular Pressure and Ocular Perfusion Pressure in Glaucoma
  - Quaranta 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,