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

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

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
2/10/1999

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

1999–2006
IOP running R 12–17 L 13–14
On Xalatan and Combigan
VF getting worse OD
Now what?

Larry 2009
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

The Questions

- Does blood flow to the optic nerve matter in glaucoma?
- Do we have an accurate, valid means of measuring blood flow to the optic nerve?
  - That is clinically useful?
- Does blood pressure matter?
- Can we affect blood flow to the optic nerve?
- Do we have any evidence that doing so improves the prognosis in glaucoma?
The Evidence Against Blood Supply as a Risk Factor for Development and/or Progression of Glaucoma

Factors NOT Predictive

- Ocular Hypertension Treatment Study
  - Migraine
  - Cerebral vascular accident
  - High OR low blood pressure
  - Use of oral Beta blockers, Calcium channel blockers
  - Diabetes
- Early Manifest Glaucoma Trial
  - 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 for progression of VF abnormalities in NTG AJCN 201; 131:499-708
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?)

The Evidence For Blood Supply as a Risk Factor for Development of Glaucoma
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 Oph; 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.

Systolic BP and Glaucoma

- 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
- Barbados Eye Study
  - Low SBP was a risk factor for incidence of OAG
- EMGT: Low SBP was a predictor for progression
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

Consensus Points

- Blood Pressure is positively correlated with IOP.
- It is unclear whether the level of BP is a risk factor for having or progressing OAG in an individual patient.
- 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.

Conclusion

“The relationship among BP, IOP and development of OAG is complex and requires further investigation.”
Ocular blood flow refers to the distribution of oxygenated blood throughout the vasculature in the eye.\(^1\)

Ocular perfusion pressure (OPP) refers to the pressure available to drive blood through the intraocular vasculature, with the degree of perfusion being influenced by the resistance to flow, which is a function of the vessel caliber or the vessel tone.\(^2\)

Ocular blood flow exhibits autoregulation, which is characterized by local vascular constriction or dilatation causing an increase or decrease in vascular resistance, thereby maintaining a constant nutrient supply in response to perfusion pressure changes\(^3\).

\(^1\) Costa VT, Harris A, Anderson Dot al Acta Ophthal. 2014: 92: e252–e266
\(^2\) Caprioli J & Coleman AL; AJO 2010 149: 704–712
OPP and Glaucoma: Population Studies

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


OPP: Proyecto VER

![Graph showing percentage of双眼压与OCT的关系](image)


OPP in EMGT

- Randomized clinical trial comparing no treatment to treatment for initially diagnosed glaucoma (entire cohort followed for progression)
- In patients with higher baseline IOP:
  - h/o CVD increased risk (HR 2.75, CI 1.44-5.26)
  - Lower SPP increased risk (HR 1.55, CI 1.02-2.35)
- In patients with lower baseline IOP:
  - Higher systolic BP decreased risk (HR .44, CI .2-.97)

WGA Consensus Points

- Low ocular perfusion pressure (OPP) is associated with increased prevalence of OAG

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.


The Question

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

Consensus Point:
- Reviewed methods of measuring OBF
- Ocular pulse analyzer
- Doppler US, etc.
- At the present time, there is no single method for measuring all aspects of ocular blood flow and its regulation in glaucoma


That was then
This is Now
OCTA in Glaucoma
Mark

- 59yoWM treated for NTG
- Baseline IOP by report 19 OU
- Currently using Travatan-Z, dorzolamide-timolol OS only
- Allergic to brimonidine
- S/P trabeculectomy OD 2-16-17
- IOP R 07 L 15
What does the visual field look like?
OCTA Vessel Density (VD) in Healthy, Glaucoma Suspect, and Glaucoma Eyes

- 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-μm wide annulus around the disc)
  - whole-image vessel density (wiVD) (entire 4.54.5-mm scan field)
- Areas under the receiver operating characteristic curves (AUROC) were used to evaluate diagnostic accuracy
- For differentiating between glaucoma 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).


Relationship between OCTA Vessel Density and Severity of VF Loss in Glaucoma

- 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 (55.3%, 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;123:2498-2508

Can we affect blood flow to the optic nerve?
A number of studies have found no significant benefits from the use of calcium antagonists in glaucoma.

"Calcium antagonists can cause nocturnal hypotension, which, in addition to other systemic side effects, adversely affects the blood flow in the optic nerve head."

"In view of these considerations, there seems to be little scientific basis for use of calcium channel blockers in glaucoma treatment."

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Timolol\(^1,4\) and brimonidine\(^2\) do NOT lower nocturnal IOP

PGA's\(^3,1,6\), CAI's\(^4\) 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\(^5\)

3. Liu J, Weinreb RN et al. AD 2008:44:1133−1136
OPP and Glaucoma Medications

- Cross over study of effect of different classes of IOP lowering meds on DPP
  - PGA 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 brimatoprost 0.01% QD or timolol 0.5% bid
- Measured IOP, BP, HR, OPP after 8 weeks
- Mean 24h IOP was significantly lower after 8 weeks of treatment with bimatoprost 0.01% than timolol 0.5% bid (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 \(-2.3 \text{ mmHg} (p = 0.0002)\) by bimatoprost and by \(-1.1 \text{ mmHg} \) by timolol 0.5% bid (\( p = 0.06 \)).
- 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.


Conclusion

- Both Bimatoprost 0.01% and Timolol 0.5% are effective in reducing the mean 24h IOP from an untreated baseline but Bimatoprost 0.01% is more effective than timolol 0.5% throughout the 24h.
- Timolol 0.5% effect on IOP is reduced during the night hours and is associated with reduced BP, HR and ocular perfusion pressure.

Patients using topical beta blockers had:
- Lower minimum nocturnal heart rate
- Lower minimum nocturnal DBP
- Greater percentage drop in nocturnal DBP

Timolol:
- Controversial
- Most studies report no significant or rather unfavorable results.

Betaxolol:
- Reports vary: beneficial or not significant
- More favorable than Timolol


PGA’s, CAI’s

Prostaglandin Analogues: Latanoprost, Bimatoprost and Travoprost
- Generally show beneficial effects on retrobulbar hemodynamics

Carbonic Anhydrase Inhibitors (CAI’s)

Dorzolamide, Brinzolamide:
- Reports mixed but more showed positive effects on OBF
- Others showed no significant effect


Efficacy of Latanoprostene Bunod 0.024% (Vyzulta) Compared With Timolol 0.5% in Lowering IOP Over 24 Hours

- Compared the diurnal and nocturnal effects of latanoprostene bunod with timolol 0.5% solution on IOP and OPP
- 25 patients with OHTN or early OAG
- Baseline IOP and BP were measured in a sleep lab Q2H in habitual positions
- Latanoprostene QHS or timolol BID
- Mean IOP and OPP were compared for the diurnal and nocturnal periods

Low BP at night, coupled with high IOP in supine position, compromise OPP
Using systemic BP meds in the AM to minimize nocturnal hypotension makes sense
Using IOP lowering drugs that lower IOP while sleeping makes sense
Avoiding IOP meds that LOWER systemic BP at night (beta blockers, alpha agonists) makes sense

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.

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.
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 understood. Large-scale longitudinal studies would be required to evaluate the risk of glaucomatous progression in non-dippers, dippers, and extreme nocturnal BP dippers.

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.

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

Be aware of vascular health issues in our glaucoma patients.
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
  - Vasoconstriction