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

Seriously . . .

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Half of what you'll learn during training will be shown to be either dead wrong or out-of-date within 5 years .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

严重 . . .

POAG 是一种渐进性、慢性视神经病变，在成人中，其特征是伴有眼内压（IOP）和其他目前未知因素的损伤，其中视神经有先天性萎缩，视网膜神经节细胞和其轴突丢失。这种条件与前房角出现眼内窥镜视诊相关。

—ala AAO PPP

“可以由非IOP相关的创伤单独诱导视神经病变吗？” —克劳德·伯戈因

严重 . . .

DK: POAG, ???

是否有血流问题？
When do you think this editorial appeared?

May be a good introduction.

When do you think this editorial appeared?

2009

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 multilayer vascular beds of the eye.”

Consensus statement of the WGA 2009
OCT will revolutionize the diagnosis, management & understanding of glaucoma...

- Higher resolution
- Differential depth scans
- O/R applications
- Smartphone app
- OCT angiography!!!

**Optical Coherence Tomography Angiography of Optic Disc Perfusion in Glaucoma**

Yue Xu, MD, Ph.D., Wei Wei, PhD, Shuying Wang, MD, Lulu Zhang, MD, John J. Johnson, MD, Marie Polito, MD, Lee H. Lashkari, MD, Linda M. Carney, MD, Effrosyni A. Alexiou, MD

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

**Design:** Observational, cross-sectional study.

**Participants:** Twenty-four normal subjects and 19 patients with glaucoma were included.

**Methods:** A high-speed swept-source OCT angiography system was used to capture high-resolution OCT angiography images and to correlate Doppler spectral power density analysis with OCT angiography. Three surface-rendered images and the disc perfusion map were used to define the central avascular area (CVA), the inner vascular area (IVA), and the outer vascular area (OVA). The flow rate was calculated by subtracting the flow rate in the normal optic disc from the flow rate in the glaucomatous optic disc. The flow rate directly relates to the appearance (brightness) of vessel in the image.

**Results:** Optical coherence tomography angiography provided detailed vasculature without any dye or contrast enhancement injection. The flow rate was directly related to the appearance (brightness) of vessel in the image.

**Conclusion:** Optical coherence tomography angiography can be used to study blood flow and can help assess glaucomatous optic disc perfusion.
Glaucoma

Generalized and local effects.

Maybe this helps explain the asymmetry that is so prevalent in glaucoma.

Think: VF, rim tissue, PPA
Proposed mechanisms

Conclusions. There is a close link between reduced retinal blood flow and visual field loss in glaucoma that is largely independent of structural loss. Further studies are needed to elucidate the causes of the vascular dysfunction and potential avenues for therapeutic intervention. Blood flow measurement may be useful as an independent assessment of glaucoma severity. (J. Ophthalmic Vis. Sci. 2012;53:3020–3026) DOi:10.1167/jovs.11-8552

Reduced blood flow could be a consequence of neural tissue loss arising from elevated IOP.

Proposed mechanism

Reduced blood flow and elevated IOP could both lead to neural structure loss.

Proposed mechanism

Reduced blood flow could be an independent cause of VF loss.

And just 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.]

Ocular Perfusion Pressure & Glaucoma Progression – emerging paradigms

Hayreh SS. Trans Am Acad Ophthalmol. 1974;78:240-54
Is there a blood-flow problem here???


Hayreh’s papers on choroidal blood flow:

**Hey! Maybe its choroidal blood flow**

Choroidal blood flow (arbitrary units)

Hey! Maybe its choroidal blood flow. After all that seems to be the case in AMD
Implications of BF alterations with ↑↑ IOP

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

Blood supply summary

• Interindividual variation*
• Retinal nerve fiber layer
  – CRA / CRV
• Optic nerve head
  – SPCaa
  – choroidal plexus
  – blood supply is segmental

* Ultimate blood supply to RNFL and OMM is from the ophthalmic artery, a branch of the internal carotid artery

Vascular Theory of Glaucoma

Changes in ocular blood flow (OBF)

• Reduced perfusion pressure (beyond autoregulatory capacity) leading to...
  – Secondary vascular degeneration following ganglion cell / RNFL loss

Peripheral vascular dysregulation - PVD
  – which can result in reperfusion injury (RI)

• All can be IOP independent and may involve both the retinal and choroidal circulatory systems.

Schematic summary - normal

* Some variability and controversy exist over blood supply
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

Implying an IOP-independent component in glaucoma ("NTG" ??)

What are the possibilities in the absence of elevated IOP?

- Primary / Peripheral vascular dysregulation
- Inadequate ONH perfusion

Let’s try and connect the dots

Relationship of perfusion to glaucoma

- Low diastolic ocular perfusion pressure may be associated with increased risk for POAG.
- This association was confirmed in subjects treated for systemic hypertension in subgroup analysis. This may support the hypothesis that the concept of ocular perfusion pressure status may be more relevant to glaucoma pathogenesis than ocular perfusion pressure alone.

Consult the patient’s beta-blocker prescriber in the context of progressive glaucoma damage with “good” IOP control.

Primary OBF component

- Risk factors (RF) for atherosclerosis are largely parallel to increased IOP
  - age
  - smoking
  - dyslipidemia
  - systemic hypertension
  - male sex
  - obesity

Primary OBF component

- Risk factors (RF) for atherosclerosis are largely parallel to increased IOP
  - age
  - smoking
  - dyslipidemia
  - systemic hypertension
  - male sex
  - obesity
- Therefore reducing these RF reduces IOP (slightly)
  - physical exercise
  - weight loss
  - treatment of dyslipidemia
- And may increase blood flow and aqueous outflow through the TM

‘Normal Tension Glaucoma?’

- Glaucomatous disc and field changes with IOP consistently < 22
- 20% of newly diagnosed glaucoma patients have IOP < 21 mm Hg at presentation
- CAUSE ? Decreased perfusion of disc (arteriosclerosis, low BP)

‘Normal Tension Glaucoma’

Recent evidence...

Ocular Perfusion Pressure & Glaucoma Progression
Perfusion to the ONH

- **DOPP** (Diastolic ocular perfusion pressure) = DBP – IOP

(What is the number?)
- <40 is significant* - talk to the PCP
- Reduced in POAG

Alternatively, mean perfusion pressure


**Example comparing DOPP and mean OPP**

<table>
<thead>
<tr>
<th>IOP</th>
<th>DOPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>120/80</td>
<td>20</td>
</tr>
</tbody>
</table>

What IOP do we measure? diastolic

Significant difference

Which to use???

**MOPP** = 2/3[DBP = 1/3 (SBP-DBP)]-IOP

2/3[80 + 1/3 (40)] – 20 results in 42

Recent association between BP/ OPP and structural glaucoma progression

- Two greatest risk factors
  - Older age
  - Lower diastolic BP

- Structural elements assessed – ONH (rim tissue), RNFL thickness.

Emerging importance of diastolic BP

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


**Association of Open-angle Glaucoma With Perfusion Pressure Status in the Theessaloniki Eye Study**

**CONCLUSIONS:** Low diastolic ocular perfusion pressure may be associated with increased risk for POAG. This association was confirmed in subjects treated for systemic hypertension in subgroup analysis. This may support the hypothesis that the concept of ocular perfusion pressure status may be more relevant to glaucoma pathogenesis than ocular perfusion pressure alone. (Am J Ophthalmol 2013;155:843–851. © 2013 by Elsevier

*Significantly lower diastolic perfusion pressure was observed in those taking oral hypotensive medications (as in beta-blockers)*
Model of primary & secondary insults in glaucoma due to low OPP

Influences of abnormal autoregulation in glaucoma (proposed scheme)

Conclusions from previous

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 [59-61].* This improvement in technology is associated with the hope of gaining more insight into ocular BF regulation.
So, which is more important, lowered BP or elevated IOP?

Conclusions

The results show that optic nerve head blood flow is more susceptible to an ocular perfusion pressure decrease induced by lowering the blood pressure compared with that induced by increasing the intraocular pressure.

This blood flow autoregulation capacity vulnerability to low blood pressure may provide experimental evidence related to the hemodynamic pathophysiology in glaucoma.

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

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

Recent association between nocturnal BP dips and ODH in NTG

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)

Reduced perfusion - More Risk factors

• Autoregulation disturbances
• Vasospastic Disorder
• Migraine
• Increased resistance
• ✔Reduced blood flow (20 low BP) → Nocturnal hypoperfusion
• Sleep apnea syndrome


SAS – Glaucoma connection
(additional evidence)

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


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.


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


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.


<table>
<thead>
<tr>
<th></th>
<th>Glaucoma -</th>
<th>Glaucoma +</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea -</td>
<td>64,825</td>
<td>3,410</td>
<td>68,236</td>
</tr>
<tr>
<td>95.0%</td>
<td>(5.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea +</td>
<td>2,497</td>
<td>228</td>
<td>2725</td>
</tr>
<tr>
<td>91.6%</td>
<td>(8.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>67,322</td>
<td>3,638</td>
<td>70,960</td>
</tr>
</tbody>
</table>

Limitations and confounders

A new issue - translaminar intracranial pressure

Key Words

translaminar intracranial pressure - retinal perfusion - choroidal blood flow

Abstract

The choroidal circulation provides mostly in situ nutrient and oxygen to the retina. Hence, translaminar intracranial pressure (TIP) affects the choroidal blood flow. Many studies have examined the relationship between TIP and choroidal blood flow in different pathologies, such as OHS and diabetes. However, few studies have evaluated the relationship between TIP and choroidal blood flow in healthy subjects. This study aimed to determine the relationship between TIP and choroidal blood flow in healthy subjects.

Methods

A total of 30 healthy volunteers were recruited for the study. All participants underwent a complete ophthalmic examination, including the measurement of TIP using the transcranial Doppler (TCD) technique. Choroidal blood flow was measured using an optical coherence tomography (OCT)-based flowmeter. The relationship between TIP and choroidal blood flow was analyzed using linear regression analysis.

Results

The results showed a significant positive correlation between TIP and choroidal blood flow (r = 0.67, p < 0.01). In addition, the mean TIP was significantly higher in the healthy group compared to the control group (p < 0.01).

Conclusion

Our study demonstrates a significant positive correlation between TIP and choroidal blood flow in healthy subjects. This finding suggests that TIP could be used as a potential biomarker for assessing the functional status of the choroid in healthy individuals.

DHEMATOL - Review

**Title:** Hemodynamic Interactions in the Eye: A Review

**Authors:**

1. S. Anthony C. et al.

**Journal:** Ophthalmologica 2013

**Abstract:**

The choroidal circulation provides nutrients and oxygen to the retina. The choroidal circulation is also sensitive to changes in intracranial pressure (ICP). Translaminar intracranial pressure (TIP) is the pressure difference between the intracranial space and the subarachnoid space. TIP is known to affect the choroidal circulation, but the exact mechanism is not well understood. This review aims to discuss the current understanding of the relationship between TIP and choroidal circulation.

**Keywords:**

translaminar intracranial pressure, retinal circulation, choroidal blood flow, optic nerve.
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.

New directions in glaucoma treatment

• Yes, treatment
• Beyond IOP reduction, regulation of blood flow . . .
  – Systemically (regulating blood pressure and monitoring perfusion pressure)
  – Locally – endothelial-cell activity by modulating Nitric Oxide (NO) This is the NEXT BIG THING!
    • Regulation of aqueous dynamics at the trabecular meshwork by vascular modulation
      • In addition, the application of NO-donating compounds for the lowering of IOP directly

How should glaucoma be managed comprehensively?

• First, lower IOP

• 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.
The effects of antioxidants on ocular blood flow in patients with glaucoma

Alice Harris, Jodi Gross, Natchadee Moore, Thi D. Bui, Anh Huynh, Wiliy Goo and Beni Smith

Department of Ophthalmology and Visual Sciences, Duke and Marlee O’Niel Eye Institute, Duke University Medical Center, Durham, NC, USA.


Study design

• 45 patients with confirmed glaucoma on IOP-lowering treatment (placebo controlled, X-over)

• Baseline and post-administration (@ 1 month) measurements
  - IOP
  - OPP
  - Retrobulbar (ultrasound) and retinal capillary (Doppler) blood flow

Results

• Increased peak systolic and/or end diastolic velocities among the active group (but not placebo)

• Reduced vascular resistance in central retinal and short posterior ciliary arteries

• Increased superior and inferior temporal retinal artery mean blood flow

• Enhanced retinal capillary density

SO, what were they given?

How should glaucoma be managed comprehensively?

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

Table 1. Ingredients of specialized dietary supplement.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C (ascorbic acid)</td>
<td>250 mg</td>
</tr>
<tr>
<td>Tocopherol (mixed tocopherols)</td>
<td>80 mg</td>
</tr>
<tr>
<td>Retinoic acid (50% free acid, 50% ethyl ester)</td>
<td>400 mg</td>
</tr>
<tr>
<td>Vitamin B12 (methylcobalamin)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Magnesium (magnesium oxide, aspartate)</td>
<td>120 mg</td>
</tr>
<tr>
<td>N-Acetyl-D-aspartate (NAD)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Alpha-Lipoic Acid</td>
<td>200 mg</td>
</tr>
<tr>
<td>Grape Seed Extract (Red Grapes, 24% polyphenols, flavone glucosides)</td>
<td>120 mg</td>
</tr>
<tr>
<td>Omega-3 Fish Oil (Docosahexaenoic acid 100 mg, Eicosapentaenoic acid 20 mg)</td>
<td>120 mg</td>
</tr>
<tr>
<td>Milkweed leaf extract (25% anthocyanidins)</td>
<td>115 mg</td>
</tr>
<tr>
<td>Coenzyme Q10 (CoQ10)</td>
<td>30 mg</td>
</tr>
<tr>
<td>Grape seed extract (5% proanthocyanidins)</td>
<td>50 mg</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>50 mg</td>
</tr>
<tr>
<td>Phytosterol ole (480 mg omega-3), galactone, gallocatechin, lutein, zeaxanthin, lutein</td>
<td>50 mg</td>
</tr>
<tr>
<td>Flavouring, natural colour, thiamine, tocopherol</td>
<td>50 mg</td>
</tr>
</tbody>
</table>
**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

---

**Consider this:**

- Is glaucoma AION that happens over a lifetime?
- OR
- Is AION glaucoma that happens overnight?

---

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

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


Brimonidine 24-hr

Profiles of 24-hour supine IOP.
Open circles represent baseline
Solid circles represent brimonidine treatment.

Data were from the same 15 subjects as previously.

Bottom line: brimonidine does not work when patients are in the supine position

timolol, brinzolamide 24-hr (added to latanoprost monotherapy)

There was no difference in nocturnal IOP between the timolol add-on treatment and the baseline.

Addition of brinzolamide lowered the AM peak.


The holy grail of glaucoma whether it is diagnosis or management is . . .

CONTINUOUS IOP MEASUREMENT
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:

Closing thoughts

• How can IOP be monitored continuously?

• What impact may this have on management?

Thank You