Blood flow in Glaucoma – Insights and Perspectives

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California Optometric Association
Monterey 2018

Disclosures – Leo Semes, OD, FAAO

Commercial Interest	Nature of Relevant Financial Relationship	
Maculogix	Honorarium	Speaker
Science Based Health	Honorarium	Speaker
OptoVue	Honorarium	Speaker
B&L	Honorarium	Advisor
Allergan	Honorarium	Advisor
Regneneron	Honorarium	Speaker
Shire	Honorarium	Speaker
ZeaVision	Honorarium	Advisor
Reichert/Ametek	Honorarium	Speaker
HPO	Stock options	Advisor

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Half of what you'll learn during training will be shown to be either dead wrong or out-of-date within 5 years .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

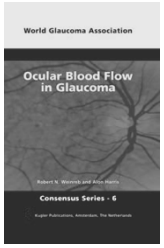
…the trouble is that nobody can tell you which half.

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

How many states have only four letters?

- Clue: Ohio is not one

Seriously . . .

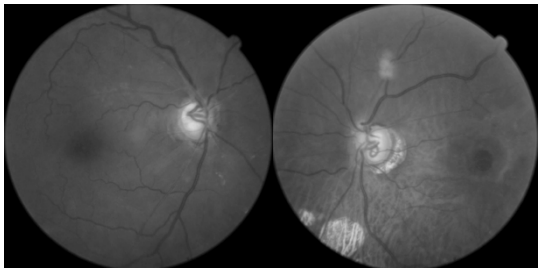
POAG is a progressive, chronic optic neuropathy in adults in which intraocular pressure (IOP) *and other currently unknown factors* contribute to damage and in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated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

–ala AAO PPP

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



DX: POAG, ??? Is there a blood-flow problem here???

Blood pressure and glaucoma

V P Costa,[1,2] E S Arcieri,[1,3] A Harris[4]

ABSTRACT

Although intraocular pressure (IOP) is considered the main risk factor for the development of glaucoma and the only parameter subject to treatment, there is sufficient evidence to suggest that glaucoma may continue to progress despite lowering patients' IOP to targeted levels. Several studies have implicated vascular risk factors in the pathogenesis of glaucoma. Among them, blood pressure (BP) and ocular perfusion pressure have become increasingly important. Although clinicians cannot currently visualise ocular blood flow directly, they can easily measure glaucoma patients' BP and IOP to calculate their ocular perfusion pressure and quantify the vascular changes. The purpose of this review article is to discuss the relationship between BP and IOP, BP and glaucoma, and perfusion pressure and glaucoma. We discuss the importance of autoregulation to maintain the adequate perfusion of the optic nerve head, and suggest that ocular perfusion pressure and its fluctuation may be parameters that need to be measured in glaucoma patients.

18.6 mm Hg for diastolic BP levels of ⩾120 mm Hg. The mean IOP in right eyes increased by 0.28 mm Hg for each 10 mm Hg increase in systolic BP and by 0.46 mm Hg for each 10 mm Hg increase in diastolic BP.

In the Barbados Eye Study,[25 28 29] multivariate regression analysis revealed significant associations between IOP and both systolic ($p<0.001$) and diastolic BP. Dielemans *et al*[30] examined the longitudinal relationship between systemic hypertension and change in IOP over 4 years in residents of Barbados aged ⩾40 years. Overall, the mean IOP increased by 2.5 (SD 3.9) mm Hg in black participants during the 4-year period of follow-up. Participants with elevated systolic and diastolic BP at baseline, or those receiving antihypertensive therapy had greater increases in IOP than did others.

Klein *et al*[26] investigated the association between change in systemic BP and change in IOP in Beaver Dam. Five years after baseline, the authors

When do you think this editorial appeared?

CONCLUSION

For years, fierce discussions have occurred between supporters of the mechanical and vascular theories for the pathogenesis of glaucoma. The concept of OPP and the identification of this as an important risk factor for the development and progression of glaucoma brought together the vascular and mechanical components of glaucoma. We believe that it is the balance between IOP and BP, influenced by the autoregulatory capacity of the eye, that determines whether an individual will develop optic nerve damage. However, further research is required to evaluate the importance of OPP and its fluctuation as parameters to be measured in glaucoma patients.

Review

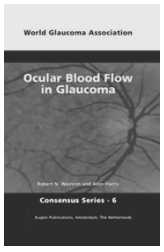
2009

Ocular Blood Flow and glaucoma?

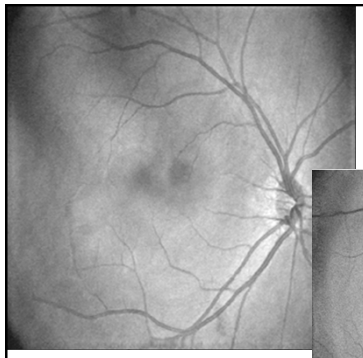
State of the science 2009

"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 multiple vascular beds of the eye."

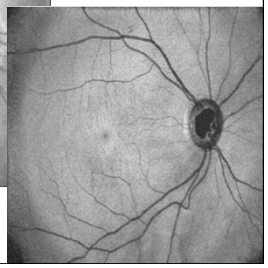


Consensus statement of the WGA 2009



AVANTI RTVUE XR

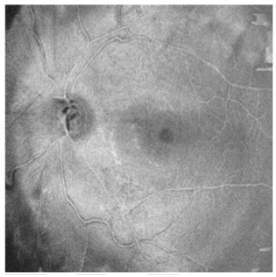
Wide Field Enface OCT ™



40º 3D En Face Reference

optovue

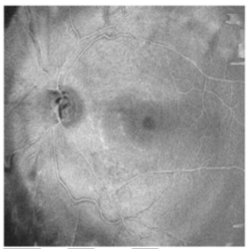
Widefield *VS*



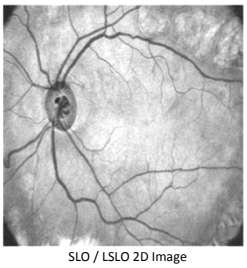
Optovue Widefield-Enface OCT

Multi-layer assessment of pathology – even in the periphery

Widefield 3D OCT *VS* Widefield SLO



Optovue Widefield-Enface OCT



SLO / LSLO 2D Image

Multi-layer assessment of pathology – even in the periphery

OCT will revolutionize the diagnosis, management & understanding of glaucoma…

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

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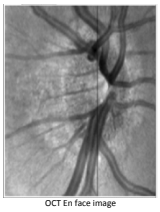
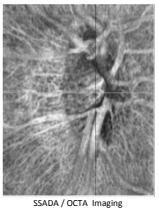
XR Avanti MCT with OCTA[1]

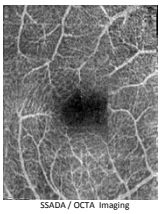


OCT En face image



SSADA / OCTA Imaging

Detailed vasculature of the fovea *without any dye or contrast enhancement injection*



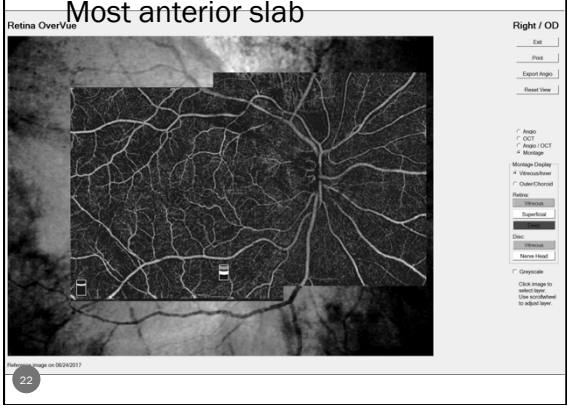
SSADA / OCTA Imaging

Flow rate directly relates to appearance (brightness) of vessel in the image[2]

*Images courtesy of David Huang, M.D. OHSU.

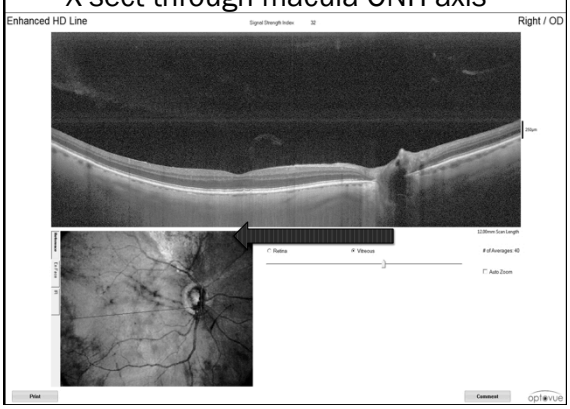
1

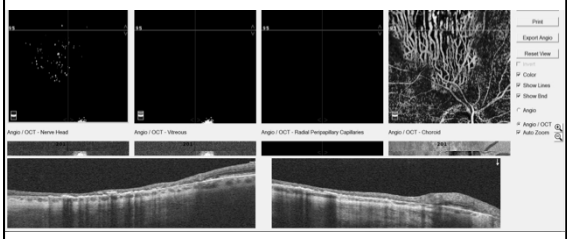
Most anterior slab



22

X-sect through macula-ONH axis





note area above ONH with demonstrable RPE loss and prominence of choroidal vasculature. AND, absence of superficial as well as deep retinal capillary plexuses

Compare with OCT X-section showing thinned retina.

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Optical Coherence Tomography Angiography of Optic Disc Perfusion in Glaucoma

Yali Jia, PhD,[1] Eric Wei, BS,[1] Xiaogang Wang, MD,[1] Xinbo Zhang, PhD,[1] John C. Morrison, MD,[1] Manasi Parikh, MD,[1] Lori H. Lombardi, MD,[1] Devin M. Gattey, MD,[1] Rebecca L. Armour, MD,[1] Beth Edmunds, MD,[1] Martin F. Kraus, MS,[2,3] James G. Fujimoto, PhD,[3] David Huang, MD, PhD[1]

2014

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, cross-sectional study.

Participants: Twenty-four normal subjects and 11 patients with glaucoma were included.

Methods: One eye of each subject was scanned by a high-speed 1050-nm–wavelength swept-source OCT instrument. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to compute 3-dimensional optic disc angiography. A disc flow index was computed from 4 registered scans. Confocal scanning laser ophthalmoscopy (cSLO) was used to measure disc rim area, and stereo photography was used to evaluate cup/disc (C/D) ratios. Wide-field OCT scans over the discs were used to measure retinal nerve fiber layer (NFL) thickness.

Main Outcome Measures: Variability was assessed by coefficient of variation (CV). Diagnostic accuracy was assessed by sensitivity and specificity. Comparisons between glaucoma and normal groups were analyzed by Wilcoxon rank-sum test. Correlations among disc flow index, structural assessments, and visual field (VF) parameters were assessed by linear regression.

Results: In normal discs, a dense microvascular network was visible on OCT angiography. This network was visibly attenuated in subjects with glaucoma. The intra-visit repeatability, inter-visit reproducibility, and normal population variability of the optic disc flow index were 1.2%, 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 100% using an optimized cutoff. The flow index was highly correlated with VF pattern standard deviation ($R^2 = 0.752$, $P = 0.001$). These correlations were significant even after accounting for age, C/D area ratio, NFL, and rim area.

Conclusions: Optical coherence tomography angiography, generated by the new SSADA, repeatably measures optic disc perfusion and may be useful in the evaluation of glaucoma and glaucoma progression. *Ophthalmology 2014;121:1322-1332 © 2014 by the American Academy of Ophthalmology.*

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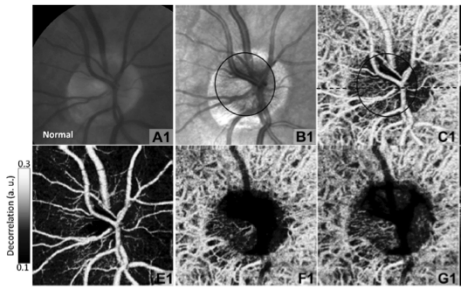
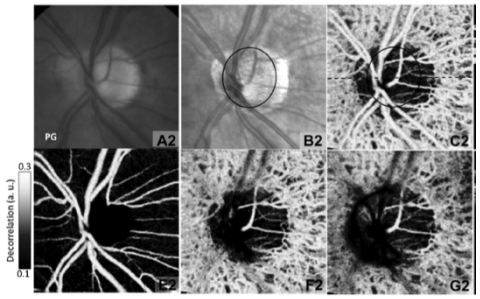
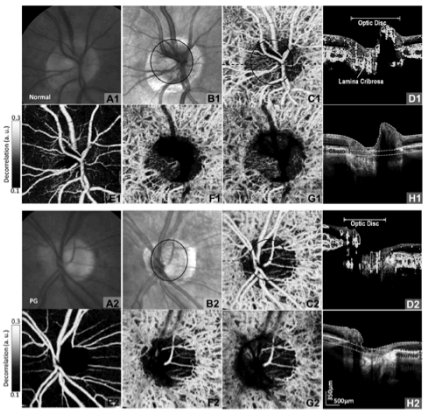
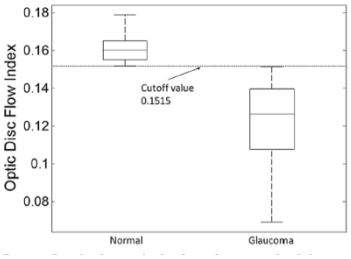




Glaucoma





Generalized and

local effects. . . .

CAPILLARY DENSITY AND RNFL THICKNESS COMPARISON

33 POAG pts. with VF depressions unilaterally *MD = -3.91 +/- 3.09 and normal fellow eye (MD = -0.2 +/- 0.9)

- whole image vessel density (wiVD),
- circumpapillary vessel density (cpVD), and
- parafoveal vessel density (pfVD)

Mean wiVD in unaffected eyes of patients with POAG was higher than in their fellow affected eyes but lower than in healthy eyes (P < 0.001).

Mean circumpapillary RNFL (cpRNFL) thickness, mGCC thickness were also higher than those measurements in fellow eyes.

"OCT-A measures detect changes in retinal microvasculature before VF damage is detectable in patients with POAG, and these changes may reflect damage to tissues relevant to the pathophysiology of glaucoma."

Yarmohammadi A, et al. Peripapillary and Macular Vessel Density in Patients with Primary Open-Angle Glaucoma and Unilateral Visual Field Loss. Ophthalmology. Volume 125, Issue 4, **April 2018**, Pages 578-587

CHOROIDAL MICROVASCULAR DROPOUT
(FOCAL SECTORAL CAPILLARY DROPOUT WITH NO VISIBLE MICROVASCULAR NETWORK IDENTIFIED IN THE CHOROIDAL LAYER)

32 Patients with an initial parafoveal scotoma (IPFS) within a 10° radius in 1 hemifield and,

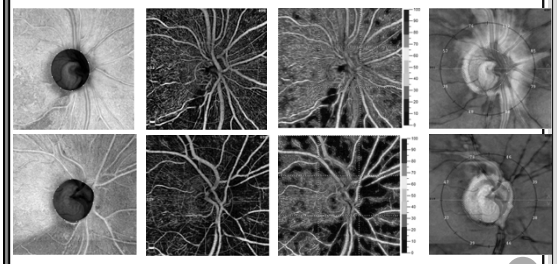
42 POAG patients with an initial nasal step (INS) within the nasal periphery outside 10° of fixation in 1 hemifield.

Microvasculature dropout (MvD) was observed in 25 of 32 eyes (78.1%) in the IPFS group, but in only 1 of 42 eyes (2.4%) in the INS group (P < 0.001).

"The presence of MvD in the parapapillary choroid was a strong predictor for IPFS."

Lee EJ, et al. Central Visual Field Damage and Parapapillary Choroidal Microvasculature Dropout in Primary Open-Angle Glaucoma Ophthalmology Volume 125, Issue 4, **April 2018**, Pages 588-596.

ANGIOANALYTICS APPROVED JUNE 2018



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2014

Retinal Blood Flow in Glaucomatous Eyes with Single-Hemifield Damage

Mitra Sehi, PhD,[1] Iman Goharian, MD,[2] Ranjith Konduru, MBBS,[2] Ou Tan, PhD,[2] Soumya Srinivas, MBBS,[2] Srinivas R. Sadda, MD,[2] Brian A. Francis, MD, MS,[2] David Huang, MD, PhD,[2] David S. Greenfield, MD[2]

Conclusions: In glaucomatous eyes with single-hemifield damage, the RBF is significantly reduced in the hemisphere associated with the abnormal hemifield. Reduced RBF is associated with thinner RNFL and GCC in the corresponding abnormal hemisphere. Reduced RBF and RNFL and GCC loss also are observed in the perimetrically normal hemisphere of glaucomatous eyes.

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

Think: VF, rim tissue, PPA . . . .

Glaucoma

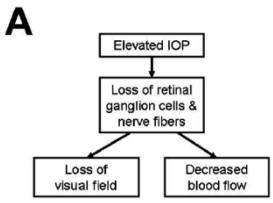
2012

Relationship among Visual Field, Blood Flow, and Neural Structure Measurements in Glaucoma

John C. Hwang,[1] Ranjith Konduru,[1] Xinbo Zhang,[2] Ou Tan,[2] Brian A. Francis,[1] Rohit Varma,[1] Mitra Sehi,[3] David S. Greenfield,[3] SriniVas R. Sadda,[1] and David Huang[2]

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. (*Invest Ophthalmol Vis Sci.* 2012;53:3020–3026) DOI:10.1167/iovs.11-8552

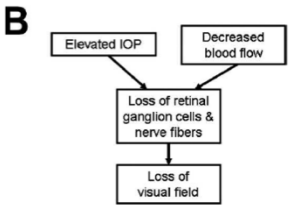
Proposed mechanisms



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

(*Invest Ophthalmol Vis Sci.* 2012;53:3020–3026)

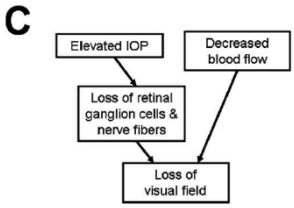
Proposed mechanism



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

(*Invest Ophthalmol Vis Sci.* 2012;53:3020–3026)

Proposed mechanism



Reduced blood flow could be an independent cause of VF loss

(*Invest Ophthalmol Vis Sci.* 2012;53:3020–3026)

And more evidence…

- 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.]

Keenan TD, Goldacre R, Goldacre MJ. Associations between primary open angle glaucoma, Alzheimer's disease and vascular dementia: record linkage study. Br J Ophthalmol. 2015 Apr;99(4):524-7.

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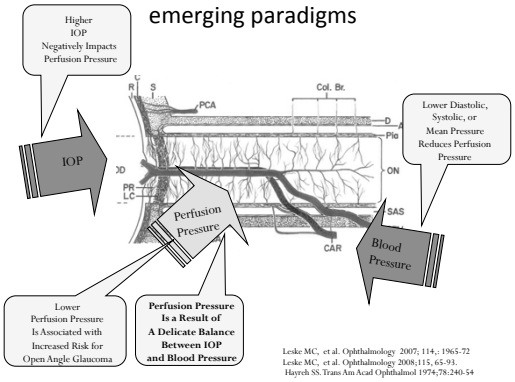
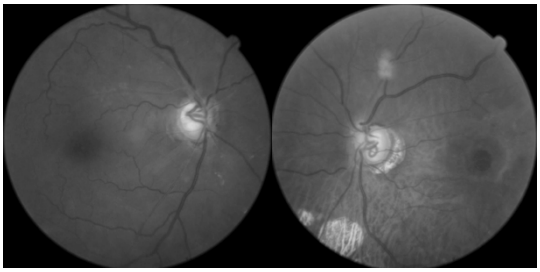
Ocular Perfusion Pressure & Glaucoma Progression – emerging paradigms

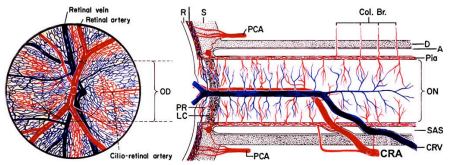




DX: POAG, ???

Is there a blood-flow problem here???

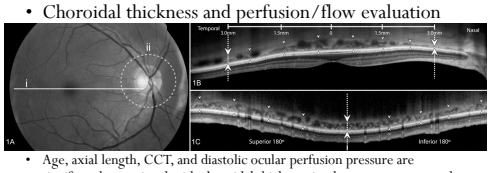
Optic Nerve HEAD anatomy – blood flow considerations



Hayreh SS. Ischemic optic neuropathy. Prog Ret Eye Res. 2009;28: 34–62

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.

•Maul EA, Friedman DS, Chang DS, Boland MV, Ramulu PY, Jampel HD, Quigley HA. Choroidal thickness measured by spectral domain optical coherence tomography: factors affecting thickness in glaucoma patients. Ophthalmology. 2011 Aug;118(8):1571-9.

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Hey! Maybe its choroidal blood flow

Progress in Retinal and Eye Research 31 (2012) 377–406

Contents lists available at SciVerse ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease

Joanna Kur [a,1], Eric A. Newman [a,*,1], Tailoi Chan-Ling [b,*,1]

[a] Department of Neuroscience, University of Minnesota, Minneapolis, MN 55455, USA
[b] Department of Anatomy, School of Medical Sciences and Bosch Institute, University of Sydney, NSW 2006, Australia

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Available online 3 May 2012

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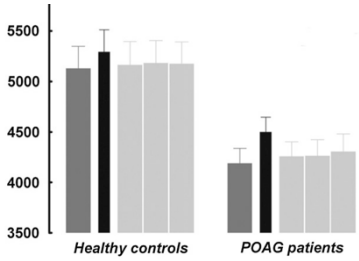
Blood flow
Retina
Choroid
Regulation
Functional hyperemia
Autoregulation
Pathology
Diabetic retinopathy
Microvasculature
Review

ABSTRACT

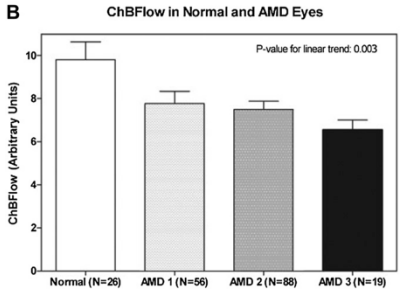
We review the cellular and physiological mechanisms responsible for the regulation of blood flow in the retina and choroid in health and disease. Due to the intrinsic light sensitivity of the retina and the direct visual accessibility of fundus blood vessels, the eye offers unique opportunities for the non-invasive investigation of mechanisms of blood flow regulation. The ability of the retinal vasculature to regulate its blood flow is contrasted with the far more restricted ability of the choroidal circulation to regulate its blood flow by virtue of the absence of glial cells, the markedly reduced pericyte ensheathment of the choroidal vasculature, and the lack of intermediate filaments in choroidal pericytes. We review the cellular and molecular components of the neurovascular unit in the retina and choroid, techniques for monitoring retinal and choroidal blood flow, responses of the retinal and choroidal circulation to light stimulation, the role of capillaries, astrocytes and pericytes in regulating blood flow, putative signaling mechanisms mediating neurovascular coupling in the retina, and changes that occur in the retinal and choroidal circulation during diabetic retinopathy, age-related macular degeneration, glaucoma, and Alzheimer's disease. We close by discussing issues that remain to be explored.

Choroidal blood flow (arbitrary units)



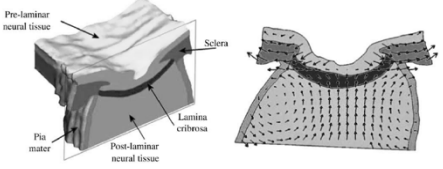
Progress in Retinal and Eye Research 31 (2012) 377–406

Hey! Maybe its choroidal blood flow. After all that seems to be the case in AMD



Progress in Retinal and Eye Research 31 (2012) 377–406

Implications of BF alterations with ↑↑ IOP



Note: increased IOP induces

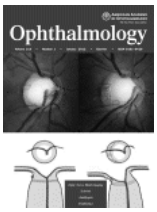
- •posterior rotation of the peripapillary sclera
- •flattening of the cup floor
- •thinning of the lamina cribrosa and the prepapillary neural tissue and
- •anterior movement of the central optic nerve relative to the LC

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

Sigal I, Ethier CR. Biomechanics of the optic nerve head. Exp Eye Res. 2009; 88,799-807 .

Structural evaluation –diagnosis
enhanced depth imaging

- Lamina cribrosa evaluation
- Emerging investigations: CSF pressure (see: later)



Park HY, Jeon SH, Park CK. Enhanced depth imaging detects lamina cribrosa thickness differences in normal tension glaucoma and primary open-angle glaucoma. Ophthalmology. 2012 Jan;119(1):10-20.

Park SC, De Moraes CG, Teng CC, Tello C, Liebmann JM, Ritch R. Enhanced depth imaging optical coherence tomography of deep optic nerve complex structures in glaucoma. Ophthalmology. 2012 Jan;119(1):3-9.

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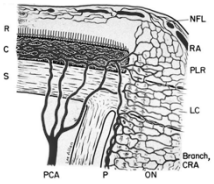
Blood supply summary

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

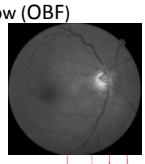


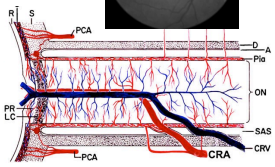
❖ *Ultimate blood supply to RNFL and ONH is from the ophthalmic artery, a branch of the internal carotid artery*

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

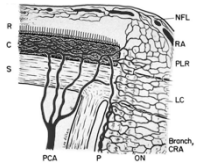




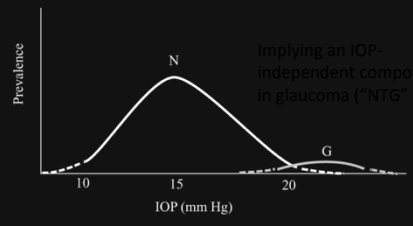
Vascular Theory of Glaucoma

Changes in ocular blood flow (OBF)

- 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.***



Distribution of IOP in a general population*

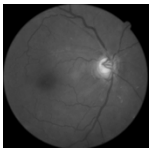


Implying an IOP-independent component in glaucoma ("NTG" ???)

N=nonglaucoma; G=glaucoma
*Dotted lines represent areas of uncertainty.
Shields MB. *Textbook of Glaucoma*. 1998.

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

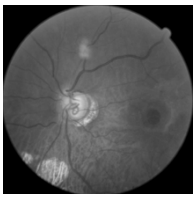
- Low diastolic ocular perfusion pressure may be associated with increased risk for POAG.
- This association was confirmed in subjects treated for systemic hypertension in subgroup analysis. This may support the hypothesis that the concept of ocular perfusion pressure **status** may be more relevant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

Am J Ophthalmol 2013;155:843–851.

Primary OBF component

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



Flammer J, Mozaffariaeh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? 2007. Surv Ohthalmol 52: S162-173.

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*

Flammer J, Mozaffariaeh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? 2007. Surv Ohthalmol 52: S162-173.

'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)

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'Normal Tension Glaucoma'

Recent evidence. . .

Primary Open-Angle Glaucoma vs Normal-Tension Glaucoma

The Vascular Perspective

Stephanie Mroczkowska, PhD; Alexandra Benavente-Perez, PhD; Anil Negi, MD; Velota Sung, FRCS(ed); Sunni R. Patel, PhD; Dotna Gherghel, PhD

Objective: To compare and contrast the presence of ocular and systemic vascular function in patients with newly diagnosed and previously untreated primary open-angle glaucoma (POAG) vs those with normal-tension glaucoma (NTG) and comparable early-stage, functional loss.

Methods: The systemic vascular function of 10 patients with POAG, 10 patients with NTG, and 20 healthy individuals serving as controls was assessed using 24-hour ambulatory blood pressure monitoring, peripheral pulse-wave analysis, and carotid intima-media thickness. Retinal vascular reactivity to flicker light was assessed using dynamic retinal vessel analysis (Imedos, GmbH).

Results: Compared with controls, patients with POAG and those with NTG exhibited similarly increased nocturnal systemic blood pressure variability ($P = .01$), peripheral arterial stiffness ($P = .02$), carotid intima-media thickness ($P = .04$), and reduced ocular perfusion pressure ($P < .001$). Furthermore, on dynamic retinal vessel analysis, both glaucoma groups exhibited steeper retinal arterial constriction slopes after cessation of flicker ($P = .007$) and a similarly increased fluctuation in arterial and venous baseline diameter ($P = .008$ and $P = .009$, respectively) compared with controls.

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.

JAMA Ophthalmol. 2013;131(1):36-43. Published online September 10, 2012. doi:10.1001/2013.jamaophthalmol.1

59

'Normal Tension Glaucoma'

Recent evidence. . .

Primary Open-Angle Glaucoma vs Normal-Tension 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.

JAMA Ophthalmol. 2013;131(1):36-43. Published online September 10, 2012. doi:10.1001/2013.jamaophthalmol.1

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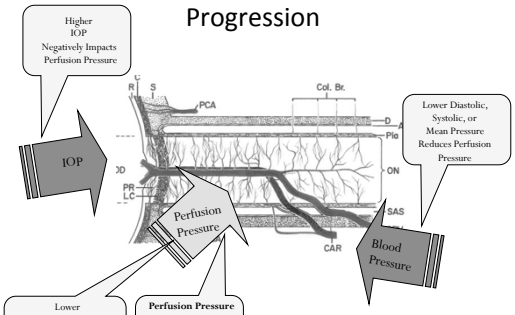
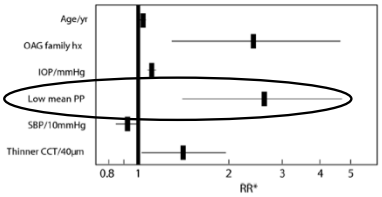
Ocular Perfusion Pressure & Glaucoma Progression



Leske MC, et al. Ophthalmology 2007; 114,: 1965-72
Leske MC, et al. Ophthalmology 2008;115, 65-93.
Hayreh SS. Trans Am Acad Ophthalmol 1974;78:240-54

POAG Risk Factors 9-year BES



mean perfusion pressure = *2/3(mean arterial pressure)* - IOP

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

Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B; BESs Study Group. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology. 2008 ; 115: 85-93.

62

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

*Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B; BESs Study Group. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology. 2008 ; 115: 85-93.

63

Perfusion to the ONH

Example comparing DOPP and mean OPP
120/80 IOP = 20; DOPP = **60** [80-20]

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**

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Glaucoma

Static Blood Flow Autoregulation in the Optic Nerve Head in Normal and Experimental Glaucoma

Lin Wang, Claude F. Burgoyne, Grant Cull, Simon Thompson, and Brad Fortune
Devers Eye Institute, Legacy Research Institute, Portland, Oregon

regulated within range of OPP approximately 41 mm Hg and above. Chronic IOP elevation causes no remarkable change to the static autoregulation within the ONH of EG eyes.

2014 (monkeys)

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.

McGlynn MM, Erlich JR, Marlow ED, et al. Association of blood and ocular perfusion pressure with structural glaucomatous progression by flicker chronoscopy. Br J Ophthalmol 2013. Published online September 24, 2013

Emerging importance of diastolic BP

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

McGlynn MM, Erlich JR, Marlow ED, et al. Association of blood and ocular perfusion pressure with structural progression in glaucoma as measured by flicker chronoscopy. Br J Ophthalmol. 2013.

Br J Ophthalmol published online September 24, 2013
doi: 10.1136/bjophthalmol-2013-303655

67

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

2013,

FOTIS TOPOUZIS, M. ROY WILSON, ALON HARRIS, PANAYIOTA FOUNTI, FEI YU, ELEFTHERIOS ANASTASOPOULOS, THEOFANIS PAPPAS, ARCHIMIDIS KOSKOSAS, ANGELIKI SALONIKIOU, AND ANNE L. COLEMAN

• 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)

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

	In Subjects Without Antihypertensive Treatment				In Subjects With Antihypertensive Treatment			
Effect	N	OR	95% CI	*P* Value[i]	N	OR	95% CI	*P* Value[i]
Association with OAG								
DPP (per 10 mm Hg) (unadjusted)	1039[a]	0.72	0.57-0.92	**.008**	1212[c]	0.78	0.66-0.93	**.006**
DPP (per 10 mm Hg) (adjusted)[f]		1.05	0.81-1.35	.731		0.83	0.68-1.01	.062
Association with POAG[j]								
DPP (per 10 mm Hg) (unadjusted)	922[b]	0.80	0.59-1.07	.13	1060[d]	0.69	0.56-0.85	**<.001**
DPP (per 10 mm Hg) (adjusted)[f]		0.98	0.72-1.33	.891		0.78	0.62-0.97	**.028**
Association with PEXG[j]								
DPP (per 10 mm Hg) (unadjusted)	117	0.76	0.51-1.13	.18	152[e]	1.10	0.79-1.52	.58
DPP (per 10 mm Hg) (adjusted)[f]		1.39[g]	0.81-2.37	.235		0.90[h]	0.58-1.41	.653

Available online at www.sciencedirect.com
SciVerse ScienceDirect
Current Opinion in Pharmacology

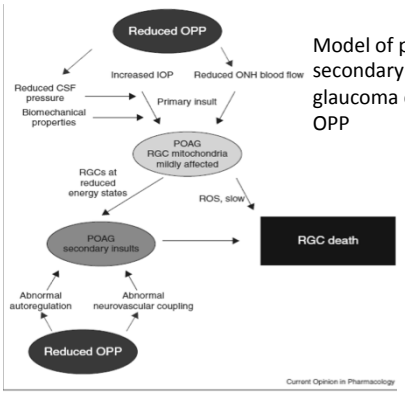
2013, **Ocular perfusion pressure and ocular blood flow in glaucoma**
A Popa Cherecheanu[1,2], G Garhofer[1], D Schmidl[1], R Werkmeister[3] and L Schmetterer[1,3]

Glaucoma is a progressive optic neuropathy of unknown origin. It has been hypothesized that a vascular component is involved in glaucoma pathophysiology. This hypothesis has gained support from studies showing that reduced ocular perfusion pressure is a risk factor for the disease. The exact nature of the involvement is, however, still a matter of debate. Based on recent evidence we propose a model including primary and secondary insults in glaucoma. The primary insult appears to happen at the optic nerve head. Increased intraocular pressure and ischemia at the post-laminar optic nerve head affects retinal ganglion cell axons. Modulating factors are the biomechanical properties of the tissues and cerebrospinal fluid pressure. After this primary insult retinal ganglion cells function at a reduced energy level and are sensitive to secondary insults. These secondary insults may happen if ocular perfusion pressure falls below the lower limit of autoregulation or if neurovascular coupling fails. Evidence for both faulty autoregulation and reduced hyperemic response to neuronal stimulation has been provided in glaucoma patients. The mechanisms appear to involve vascular endothelial dysfunction and impaired astrocyte-vessel signaling. A more detailed understanding of these pathways is required to direct neuroprotective strategies via the neurovascular pathway.

elevated intraocular pressure (IOP). Reducing IOP is effective in slowing down the progression of the disease but some patients still progress despite adequately controlled IOP.

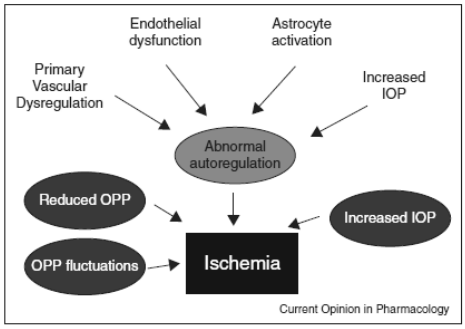
Several studies implicated vascular risk factors in the pathogenesis of glaucoma, blood pressure (BP) and ocular perfusion pressure (OPP) being the most studied. This vascular hypothesis is based on the premise that abnormal perfusion and the subsequent ischemia of the ONH play a major role in the glaucomatous damage. The OPP is the difference between arterial and venous BP. In the eye the venous pressure almost equals IOP. As such the OPP can be estimated as the difference between the arterial pressure and IOP. The relationship between BP and glaucoma is complex and controversial. On the one hand some studies indicate that systemic hypertension is a risk factor for glaucoma [1–3]. On the other hand some studies indicate that low systemic BP is a risk factor for development and progression of glaucoma. A direct and clear relationship between BP level and glaucomatous damage has, however, not been established [4]. The good irrigation of the ocular tissues is ensured by an adequate OPP depending on a complex regulation process that balances BP and the IOP. As such dealing with the concept of OPP and BP at the same time is more pertinent.

Current Opinion in Pharmacology 2013, 13:36–42 www.sciencedirect

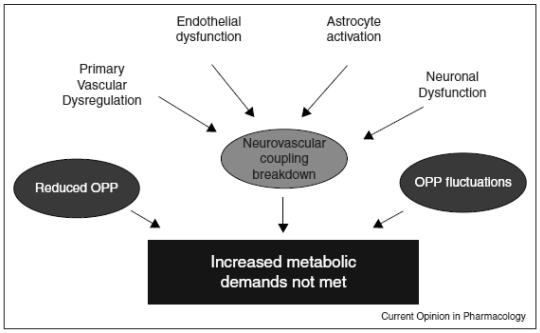


Model of primary & secondary insults in glaucoma due to low OPP

Influences of abnormal autoregulation in glaucoma (proposed scheme)



Contributing factors to abnormal *neurovascular* coupling in glaucoma



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 [59–61,62▪]. This improvement in technology is associated with the hope of gaining more insight into ocular BF regulation.

Current Eye Research, Early Online, 1–9, 2014
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ISSN: 0271-3683 print / 1460-2202 online
DOI: 10.3109/02713683.2014.924146

informa healthcare

2014

Optic Nerve Head Blood Flow Response to Reduced Ocular Perfusion Pressure by Alteration of Either the Blood Pressure or Intraocular Pressure

Lin Wang, Grant A. Cull and Brad Fortune

Devers Eye Institute, Legacy Research Institute, Portland, OR, USA

So, which is more important, lowered BP or elevated IOP?

ABSTRACT

Purpose: To test the hypothesis that blood flow autoregulation in the optic nerve head has less reserve to maintain normal blood flow in the face of blood pressure-induced ocular perfusion pressure decrease than a similar magnitude intraocular pressure-induced ocular perfusion pressure decrease.

Materials and methods: Twelve normal non-human primates were anesthetized by continuous intravenous infusion of pentobarbital. Optic nerve blood flow was monitored by laser speckle flowgraphy. In the first group of animals ($n=6$), the experimental eye intraocular pressure was maintained at 10 mmHg using a saline reservoir connected to the anterior chamber. The blood pressure was gradually reduced by a slow injection of pentobarbital. In the second group ($n=6$), the intraocular pressure was slowly increased from 10 mmHg to 50 mmHg by raising the reservoir. In both experimental groups, optic nerve head blood flow was measured continuously. The blood pressure and intraocular pressure were simultaneously recorded in all experiments.

Results: The optic nerve head blood flow showed significant difference between the two groups ($p=0.021$, repeat measures analysis of variance). It declined significantly more in the blood pressure group compared to the intraocular pressure group when the ocular perfusion pressure was reduced to 35 mmHg ($p<0.045$) and below. There was also a significant interaction between blood flow changes and the ocular perfusion pressure treatment ($p=0.004$, adjusted Greenhouse & Geisser univariate test), indicating the gradually enlarged blood flow difference between the two groups was due to the ocular perfusion pressure decrease.

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.

Keywords: blood flow, blood pressure, intraocular pressure, optic nerve

Conclusions

2014

- 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.

NOCTURNAL HYPOPERFUSION AS A GLAUCOMA RISK FACTOR

2014

Nocturnal Systemic Hypotension Increases the Risk of Glaucoma Progression

Mary E. Charlson, MD,[1] Carlos Gustavo de Moraes, MD,[2,3] Alissa Link, MPH,[1] Martin T. Wells, PhD,[4] Gregory Harmon, MD,[5] Janey C. Peterson, EdD,[1] Robert Ritch, MD,[2] Jeffrey M. Liebmann, MD[2,3]

Objective: The objective of this prospective, longitudinal study of patients with normal-tension glaucoma (NTG) was to determine whether patients with nocturnal hypotension are at greater risk for visual field (VF) loss over 12 months than those without nocturnal hypotension.

Design: Prospective, longitudinal study.

Participants: Consecutive patients with NTG with at least 5 prior VF tests were screened for eligibility.

Methods: The baseline evaluation assessed demographic and clinical characteristics, covering systemic comorbid conditions, including systemic hypertension. All oral and ophthalmologic medications were recorded. A complete ophthalmological examination was performed at baseline and follow-up. Patients had their blood pressure (BP) monitored every 30 minutes for 48 hours with an ambulatory recording device at baseline and 6 and 12 months.

Main Outcome Measures: The primary outcome was based on the global rates of VF progression by linear regression of the mean VF threshold sensitivity over time (decibels/year).

Results: Eighty-five patients with NTG (166 eyes; mean age, 65 years; 67% were women) were included. Of the 85 patients, 29% had progressed in the 5 VFs collected before study enrollment. The nocturnal mean arterial pressure (MAP) was compared with the daytime MAP. Multivariate analysis showed that the total time that sleep MAP was 10 mmHg below the daytime MAP was a significant predictor of subsequent VF progression ($P<0.02$).

Conclusions: Cumulative nocturnal hypotension predicted VF loss in this cohort. Our data suggest that the duration and magnitude of decrease in nocturnal blood pressure below the daytime MAP, especially pressures that are 10 mmHg lower than daytime MAP, predict progression of NTG. Low nocturnal blood pressure, whether occurring spontaneously or as a result of medications, may lead to worsening of VF defects. *Ophthalmology 2014;*■

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.

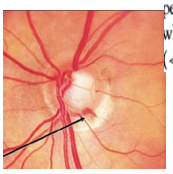
Conclusions and Guidance

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

*Recent association between nocturnal BP dips and ODH in NTG

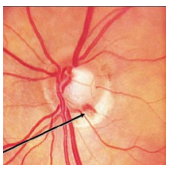
A reduction of nocturnal blood pressure (BP) in the range of 10%–20% relative to daytime BP levels is usually observed in normotensive subjects and in the majority of hypertensive patients.[22,23] This dip is termed "physiologic," while BPs that exhibit excessive (>20%) or minimal (<10%) dips at night are termed "nonphysiologic" dippers.

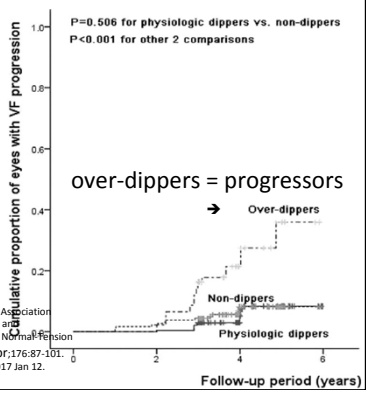
over-dippers = progressors



Kwon J, Lee J, Choi J, Jeong D, Kook MS. Association Between Nocturnal Blood Pressure Dips and Optic Disc Hemorrhage in Patients With Normal-Tension Glaucoma. Am J Ophthalmol. 2017 Apr;176:87-101. doi: 10.1016/j.ajo.2017.01.002. Epub 2017 Jan 12.

*Recent association between nocturnal BP dips and ODH in NTG





over-dippers = progressors

Kwon J, Lee J, Choi J, Jeong D, Kook MS. Association Between Nocturnal Blood Pressure Dips and Optic Disc Hemorrhage in Patients With Normal-Tension Glaucoma. Am J Ophthalmol. 2017 Apr;176:87-101. doi: 10.1016/j.ajo.2017.01.002. Epub 2017 Jan 12.

Reduced perfusion - More Risk factors

- Autoregulation disturbances
- Vasospastic Disorder
- Migraine
- Increased resistance

- ✔Reduced blood flow (2^0 low BP) → *Nocturnal hypoperfusion*

- *Sleep apnea syndrome*

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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)

Sergi M, Salerno DE, Rizzi M, et al.. Prevalence of Normal Tension Glaucoma in Obstructive Sleep Apnea Syndrome Patients. J Glaucoma. 2007; 16: 42-46.

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SAS – Glaucoma connection
(additional evidence)

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

Bendel RE, et al. Prevalence of glaucoma in patients with obstructive sleep apnoea-a cross-sectional case-series. Eye. 2007.

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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

Karakucuk S, et al. Ocular blood flow in patients with obstructive sleep apnea. Graefes Arch Clin Exp Ophthalmol. 2008; 246: 129-134.

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.

Karakucuk S, et al. Ocular blood flow in patients with obstructive sleep apnea syndrome (OSAS). Graefes Arch Clin Exp Ophthalmol. 2008 Jan; 246: 129-34.

89

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?

Lin PW, Friedman M, Lin HC, Chang HW, Pulver TM, Chin CH. Decreased retinal nerve fiber layer thickness in patients with obstructive sleep apnea/hypopnea syndrome. Graefes Arch Clin Exp Ophthalmol. 2011 Apr;249(4):585-93. Epub 2010 Oct 19.

	Glaucoma -	Glaucoma +	Total
Apnea -	64,825 (95.0%)	3,410 (5.0%)	68,236
Apnea +	2,497 (91.6%)	228 (8.4%)	2725
Total	67,322	3,638	70,960

Limitations and confounders

* Boyle-Walker M, Semes LP, Clay OJ, Fuhr P, Liu L. Sleep Apnea Syndrome Represents a Risk for Glaucoma in a Veterans' Affairs Population. ISRN Ophthalmology. Volume 2011, doi: 10.5402/2011/920767.

"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.

Stein JD, et al. The Association between Glaucomatous and Other Causes of Optic Neuropathy and Sleep Apnea. Am J Ophthalmol. 2011 Aug 17. [Epub ahead of print]

Obstructive Sleep Apnea and Increased Risk of Glaucoma

A Population-Based Matched-Cohort Study 2013,

Ching-Chun Lin, MA,[1] Chao-Chien Hu, MD,[2,3,4,5] Jau-Der Ho, MD, PhD,[2,3] Hung-Wen Chiu, PhD,[1] Heng-Ching Lin, PhD[6,7]

Purpose: Previous studies had reported an increased prevalence of glaucoma in patients with obstructive sleep apnea (OSA). However, the risk of open-angle glaucoma (OAG) among patients with OSA remains unclear. Using a nationwide, population-based dataset in Taiwan, this study aimed to examine the prevalence and risk of OAG among patients with OSA during a 5-year follow-up period after a diagnosis of OSA.
Design: A retrospective, matched-cohort study.
Participants and Controls: This study used data sourced from the Longitudinal Health Insurance Database 2000. We included 1012 subjects with OSA in the study cohort and randomly selected 6072 subjects in the comparison group.
Methods: Each subject in this study was individually traced for a 5-year period to identify those subjects who subsequently received a diagnosis of OAG. Cox proportional hazards regression was performed to calculate the 5-year risk of OAG between the study and comparison cohorts.
Main Outcome Measures: The incidence and risk of OAG between the study and comparison groups.
Results: During the 5-year follow-up period, the incidence rate per 1000 person-years was 11.26 (95% confidence interval [CI], 8.61–14.49) and 6.76 (95% CI, 5.80–7.83) for subjects with and without OSA, respectively. After adjusting for monthly income, geographic region, diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, renal disease, hypothyroidism, and the number of outpatient visits for ophthalmologic care during the follow-up period, stratified Cox proportional hazards regression revealed that the hazard ratio for OAG within the 5-year period for subjects with OSA was 1.67 (95% CI, 1.30–2.17; $P<0.001$) that of comparison subjects.
Conclusions: Our results suggest that OSA is associated with an increased risk of subsequent OAG diagnosis during a 5-year follow-up period.
Financial Disclosures(s): The authors have no proprietary or commercial interest in any of the materials discussed in this article. *Ophthalmology 2013;120:1559-1564 © 2013 by the American Academy of Ophthalmology.*

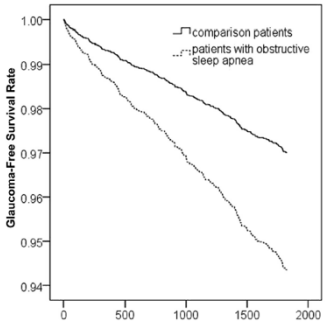

Figure 1. Open-angle glaucoma-free survival rates for patients with obstructive sleep apnea and comparison group in Taiwan

Obstructive Sleep Apnea and Increased Risk of Glaucoma

A Population-Based Matched-Cohort Study

In conclusion, our results suggest that OSA is associated with an increased risk of subsequent OAG diagnosis during the first 5 years after OSA diagnosis. We found that the hazard of receiving an OAG diagnosis during the 5-year follow-up period was 1.67 times greater in patients with OSA than in gender- and age-matched comparison subjects, after adjusting for socioeconomic characteristics and medical comorbidities. The authors hope that this study encourages clinicians to alert OSA patients of the association of between OSA and OAG as a means of raising the issue and encouraging treatment of those who need it.

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Financial Disclosures(s): The authors have no proprietary or commercial interest in any of the materials discussed in this article. *Ophthalmology 2013;120:1559-1564 © 2013 by the American Academy of Ophthalmology.*

And, the *very* latest!

Open Access Research

BMJ Open

Prevalence and risk factors of eye diseases in adult patients with obstructive sleep apnoea: results from the SLE.E.P.Y cohort study

Emilio Pedrotti,[1] Christian Luigi Demasi,[1] Enrico Bruni,[1] Francesca Bosello,[1] Paolo Plinio Di Sarro,[1] Mattia Passilongo,[1] Adriano Fasolo,[1,2] Nicola Gennaro,[3] Alessandra De Gregorio,[4] Marcello Ferrari,[5] Giorgio Marchini[1]

To cite: Pedrotti E, Demasi CL, Bruni E, *et al*. Prevalence and risk factors of eye diseases in adult patients with obstructive sleep apnoea: results from the SLE.E.P.Y cohort study. *BMJ Open* 2017;7:e016142. doi:10.1136/bmjopen-2017-016142

► Prepublication history for this paper is available online. To view these files, please visit

ABSTRACT
Objectives To assess the occurrence of glaucoma, eyelid, corneal and macular disorders in a cohort of patients with obstructive sleep apnoea (OSA) diagnosed by overnight polysomnography and to investigate into the risk factors for the above eye diseases (EDs).
Design Cross-sectional cohort study between 2014 and 2015.
Setting Unit of Respiratory Medicine and Eye Clinic of the University of Verona.
Participants 431 consecutive patients were considered

Strengths and limitations of this study

- This is a cross-sectional cohort study that provides prevalence and risk factors of eye disease in patients diagnosed with obstructive sleep apnoea using overnight polysomnography.
- Each patient had a complete ophthalmic evaluation of both eyes.
- The study was carried out in a university setting, and it was possible that our patients were a subgroup of obstructive sleep apnoea population.

And, the *very* latest!

Open Access Research

BMJ Open Prevalence and risk factors of eye diseases in adult patients with

in the general population.

The fourth most frequently observed ED was glaucoma.

A large multicentre cross-sective cohort study in France

Paolo Plinio Di Sarro,[1] Mattia Passilongo,[1] Adriano Fasolo,[1,2] Nicola Gennaro,[3] Alessandra De Gregorio,[4] Marcello Ferrari,[5] Giorgio Marchini[1]

To cite: Pedrotti E, Demasi CL, Bruni E, *et al*. Prevalence and risk factors of eye diseases in adult patients with obstructive sleep apnoea: results from the SLEEFY cohort study. *BMJ Open* 2017;**7**:e016142. doi:10.1136/bmjopen-2017-016142

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- ► The study was carried out in a university setting, and it was possible that our patients were a subgroup of obstructive sleep apnoea population.

How should glaucoma be managed comprehensively?

- First, lower IOP

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

As of Nov. 2, 2017. . .

VALEANT

Bausch + Lomb And Nicox Announce FDA Approval Of VYZULTA™ (latanoprostene Bunod Ophthalmic Solution), 0.024%

November 02, 2017

LAVAL, Quebec and SOPHIA ANTIPOLIS, France, Nov. 2, 2017 /PRNewswire/ -- Valeant Pharmaceuticals International, Inc.'s (NYSE: VRX and TSX: VRX) wholly owned subsidiary, Bausch + Lomb, a leading global eye health company, and Nicox S.A. (Euronext Paris: FR0013018124, COX), an international ophthalmic company, today announced that the U.S. Food and Drug Administration (FDA) has approved the New Drug Application (NDA) for VYZULTA™ (latanoprostene bunod ophthalmic solution, 0.024%). VYZULTA, the first prostaglandin analog with one of its metabolites being nitric oxide (NO), is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1]

Future options for medical management – *targeting the site of glaucoma, the TM*

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- latanoprostene bunod (a nitric oxide-donating compound, NO) Vyzulta (Valeant)
- FDA-approved November 2017
- MOAs:
  - relax the cellular matrix of the TM (and perhaps more distally)
  - may also act at the endothelium of TM blood vessels to constrict and therefore further open drainage pathways.

Future options for medical management – targeting the site of glaucoma, the TM

108

- Rho-kinase inhibitors (Rhopressa and Roclatan, (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%, Aerie)
  - FDA-approved December 2017
- MOAs
  - increase fluid outflow through the trabecular meshwork, (1^0 drainage)
  - increase fluid outflow through the uveoscleral pathway, (2^0 drainage)
  - reduce fluid production in the eye, and
  - reduce episcleral venous pressure (EVP).

How should glaucoma be managed comprehensively?

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- Second, consider increasing perfusion *(may be a consequence of lowered IOP)*
  - Topical treatments? (betaxolol, brimonidine, brinzolamide,
  - Gingko Biloba and other CAM interventions
  - 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

Alon Harris, Josh Gross, Nicholas Moore, Thai Do, Amelia Huang, Willy Gama and Brent Siesky

110 Glaucoma Research and Diagnostic Center, Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine, Indianapolis, IN, USA

Harris A, Gross J, Moore N, et al. The effects of antioxidants on ocular blood flow in patients with glaucoma. Acta Ophthalmol. **2017 Aug 3**. doi: 10.1111/aos. 13530. [Epub ahead of print]

ABSTRACT.

Purpose: **To investigate the effects of an antioxidant dietary supplement that includes *Ginkgo biloba*, on retinal and retrobulbar blood flow in patients with open-angle glaucoma (OAG).**

Methods: **Forty-five patients with confirmed OAG were enroled in a randomized, double blinded, placebo-controlled cross-over study. Baseline and postadministration measurements of intraocular pressure (IOP), ocular perfusion pressure (OPP), retrobulbar blood flow, and retinal capillary blood flow were non-invasively measured (ultrasound and laser Doppler modalities, respectively) before and one month after antioxidant nutraceuticals and placebo administration. Changes in measurements between the active supplement and placebo arms were evaluated using paired *t*-tests, with $p < 0.05$ considered statistically significant.**

Results: **Antioxidant supplementation produced a statistically significant increase in peak systolic and/or end diastolic blood flow velocities in all retrobulbar blood vessels compared to placebo. Vascular resistance was also reduced in central retinal and nasal short posterior ciliary arteries following antioxidant administration. Additionally, antioxidant supplementation increased superior and inferior temporal retinal capillary mean blood flow and the ratio of active to non-active retina capillaries compared to placebo.**

Conclusion: **One-month oral administration of antioxidants produced increases in biomarkers of ocular blood flow within retinal and retrobulbar vascular beds in patients with OAG.**

Key words: antioxidants – dietary supplement – glaucoma – ocular blood flow – vitamins

changes of the vasculature have been linked to OAG (Leighton & Phillips 1972; Hayreh et al. 1994; Harris et al. 2000a,b; Drance et al. 2001; Topouzis et al. 2006). Several large population-based studies have specifically identified decreased OPP (Tielsch et al. 1995; Bonomi et al. 2000) as a risk factor for OAG, and many clinical trials have found reduced retinal, choroidal, and/or retrobulbar blood flow biomarkers in OAG patients (Yin et al. 1997; Chung et al. 1999a,b; Flammer et al. 2002; Moore et al. 2008; Abegao Pinto et al. 2016).

It is important to acknowledge that currently there is no medically approved mechanism to increase ocular perfusion, nor is it established that maintaining or enhancing ocular perfusion can favourably alter the onset or progression of OAG. However, preserving sufficient ocular blood flow may theoretically have vasoprotective effects on retinal ganglion cells (Harris et al. 2000a,b). When neuroneal cells

Study design

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- 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

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- 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?

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Table 1. Ingredients of specialized dietary supplement.

Ingredient	Daily Dos
Vitamin C (ascorbic acid)	250 mg
Vitamin E (d-alpha tocopherol, mixed tocopherols)	30 IU
Vitamin B6 (pyridoxine hydrochloride)	10 mg
Folate (50% folic acid, 50% calcium folinate)	400 mcg
Vitamin B12 (methylcobalamin)	300 mcg
Magnesium (magnesium oxide, aspartate)	120 mg
Taurine	250 mg
N-Acetylcysteine (NAC)	300 mg
Alpha Lipoic Acid	200 mg
Gingko biloba Extract (leaf)(24% ginkgo flavone glycosides)	120 mg
Omega-3 Fatty Acid (Docosahexaenoic acid 100 mg, Eicosapentaenoic acid 20 mg)	120 mg
Bilberry fruit extract (25% anthocyanidins)	115 mg
Coenzyme Q10 (CoQ10)	50 mg
Grape seed extract (95% proanthcyanidins)	50 mg
Quercetin	50 mg
Flax seed oil (460 mg omega-3), gelatine, glycerine, water, beeswax, lecithin (from soya beans), lemon oil flavouring, caramel colour, and titanium dioxide	

How should glaucoma be managed comprehensively?

- Third, reduce oxidative stress (Ca^{++} blockade [BUT, not systemic β-blockers] , supplements) AND enhance blood flow!

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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 . . .

Hayreh SS. Effect of nocturnal blood pressure reduction on retrobulbar hemodynamics in glaucoma. Graefes Arch Clin Exp Ophthalmol. 2002; 240: 867-8.

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What happens to glaucoma patients during sleep?

2013,

Ahmad A. Aref

Summary

Several nighttime events including increased IOP, decreased OPP, and possibly OSA contribute to the development and progression of glaucomatous optic neuropathy. These events may explain the occurrence and progression of glaucomatous disease in the setting of seemingly controlled office-measured IOP.

Keywords

glaucoma, intraocular pressure, obstructive sleep apnea, ocular perfusion pressure

retrospective cohort studies declaring no association.

Curr Opin Ophthalmol 2013, 24:162–166
DOI:10.1097/ICU.0b013e32835c8a73

Volume 24 • Number 2 • March 2013

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 larger retrospective cohort studies declari

Curr Opin Ophthalmol 2013, 24:162–166
DOI:10.1097/ICU.0b013e32835c8a73

Volume 24 • Number 2 • March 2013

Consider this:

- Is glaucoma AION that happens over a lifetime?
-

OR

- Is AION glaucoma that happens overnight?

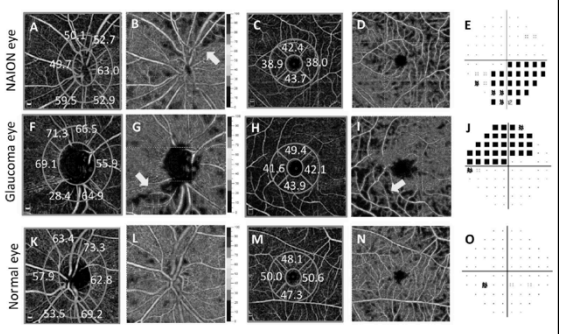


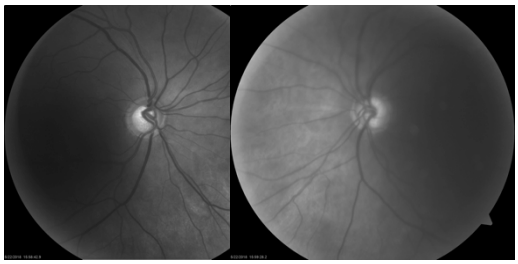
FIGURE 1. Comparison of peripapillary retinal and macular angiograms. En face optical coherence tomography angiograms (OCT-A) and vessel density (VD) (%) (A, F, K), with color-coded map (B, G, L) in the peripapillary area; OCT-A and VD (C, H, M), with color-coded map (D, I, N) in the macular area; total deviation of the visual field (E, J, O). The microvascular network of the peripapillary and macular area was attenuated (*arrow*) in the NAION eye (A–E) and OAG eye (F–J) compared with that in normal eye (K–O).

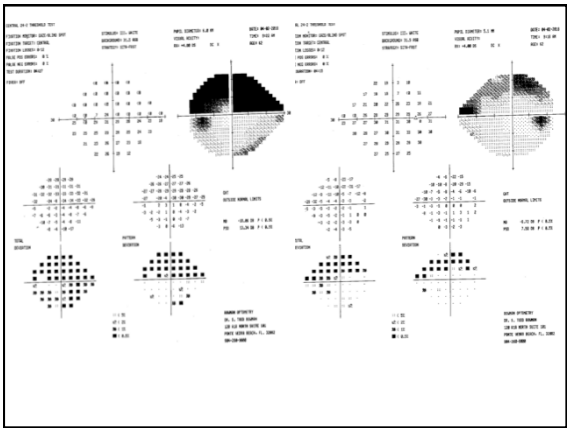
Liu C-H, et al. Comparison of the Retinal Microvascular Density Between OAG and nAION. IOVS. 2017;58:3350–3356.
DOI: 10.1167/iovs.17-22021

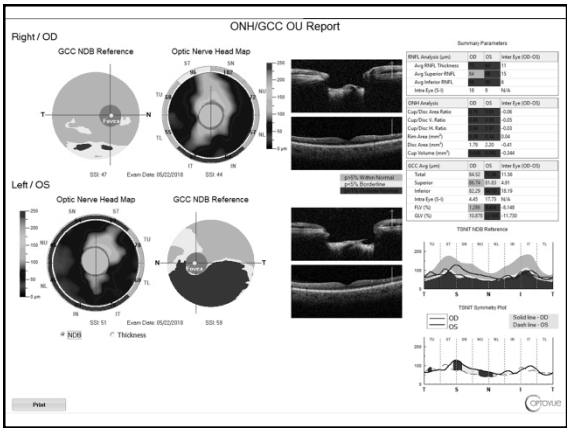
62 WM

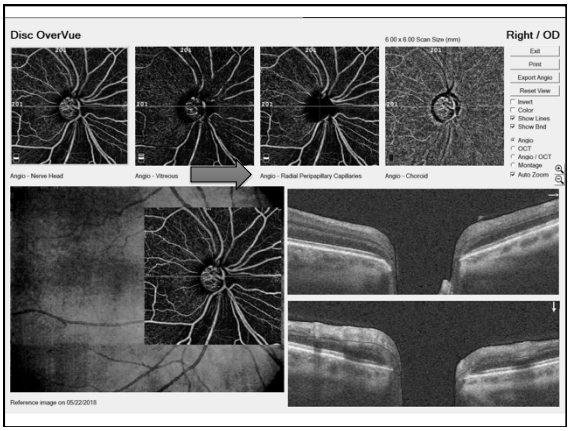
- Complained of vision loss superiorly in the left eye (May, 2018)
- VA 20/20 OD, OS; (L)RAPD 2+; IOP 11,9 mmHg.
- Seen by primary-care OD − Dx = NTG, initiated on latanoprost qhs.

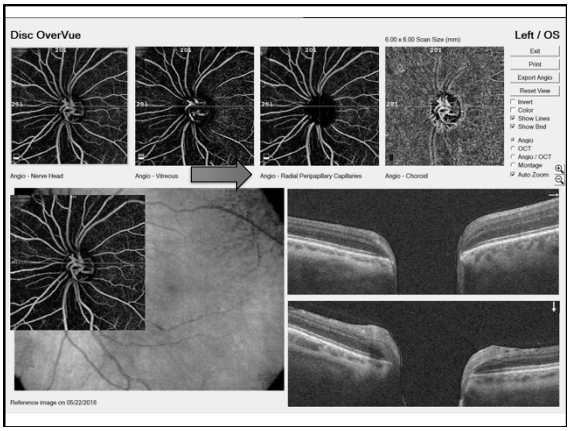
- Sent for consultation/SLT due to significant VF depressions. (June 2018)





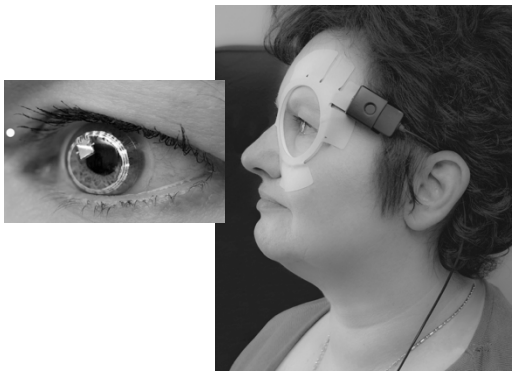






The holy grail of glaucoma whether it is diagnosis or management is . . .

CONTINUOUS IOP MEASUREMENT



Closing thoughts

- How can IOP (and BP) be monitored continuously?
- What impact may this have on management?

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States with only four letters

- Iowa
- Utah
- Mississippi
- Tennessee
- Alaska
- Hawaii
- Indiana
- Kansas

Thank You

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