

Angio OCT Glaucoma

Elliot M. Kirstein, OD, FAO

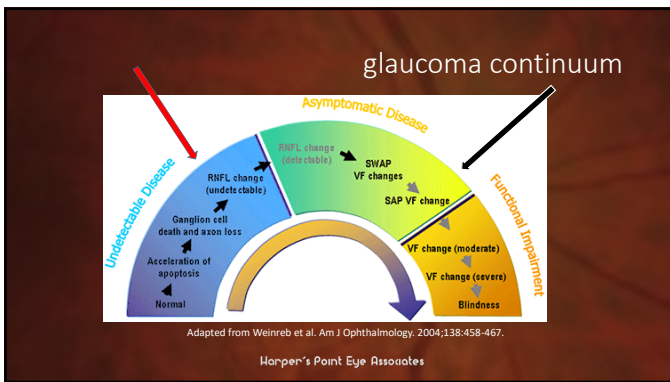
Harper's Point Eye Associates
Glaucoma and Diabetes Eye Institute
Cincinnati, Ohio

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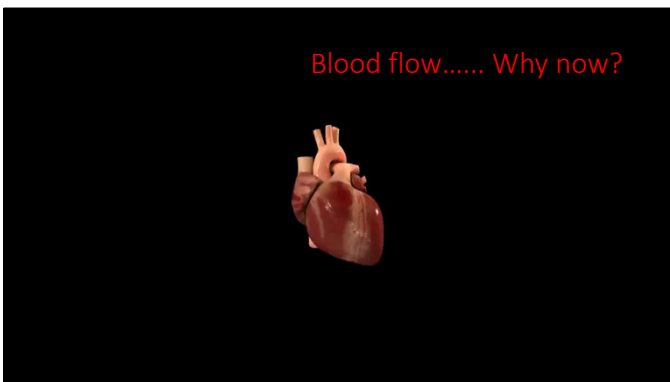
Financial Interests

- Alcon – speakers alliance
- Optovue – speakers alliance
- Reichert – speakers alliance
- Aerie – speakers alliance
- Haag Streit - speakers alliance

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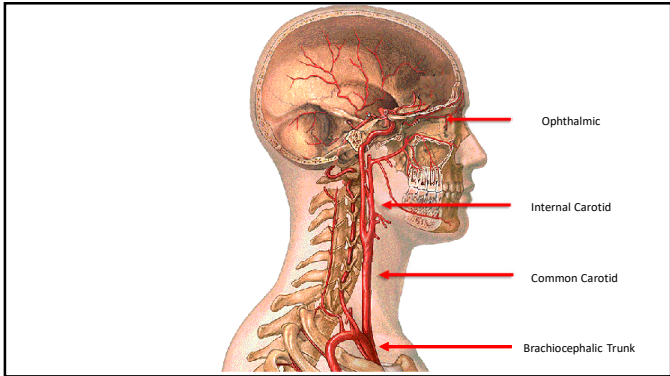
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"No problem can be solved from the same level of consciousness that created it."

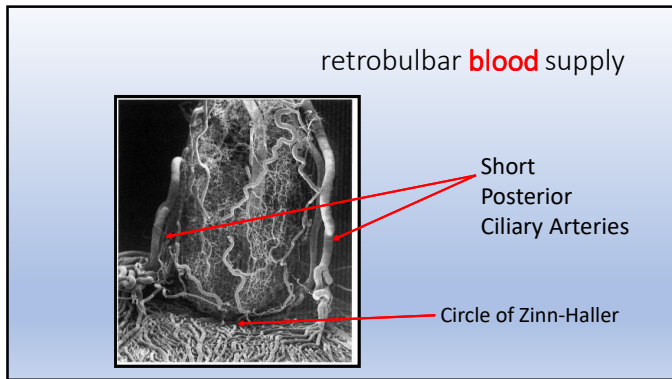
- Albert Einstein

Kirstein OD

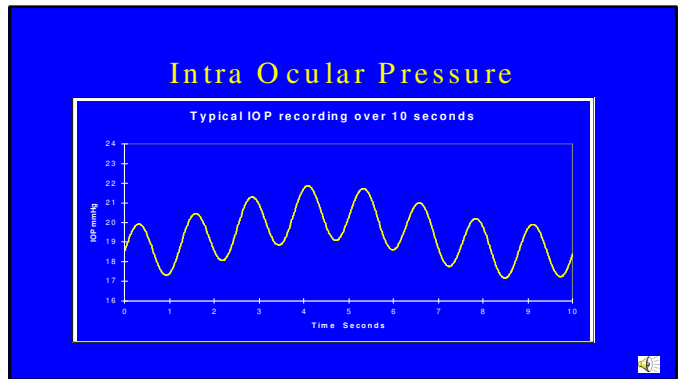
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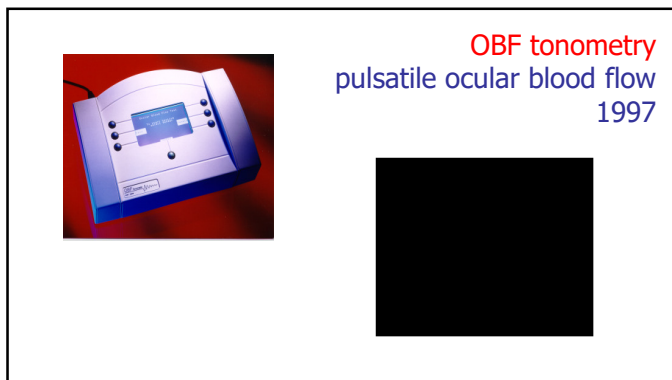
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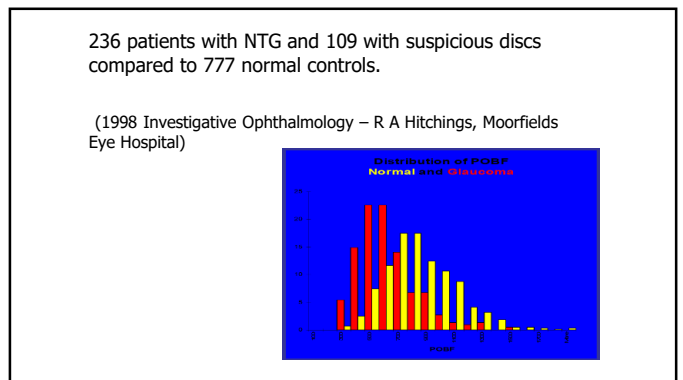
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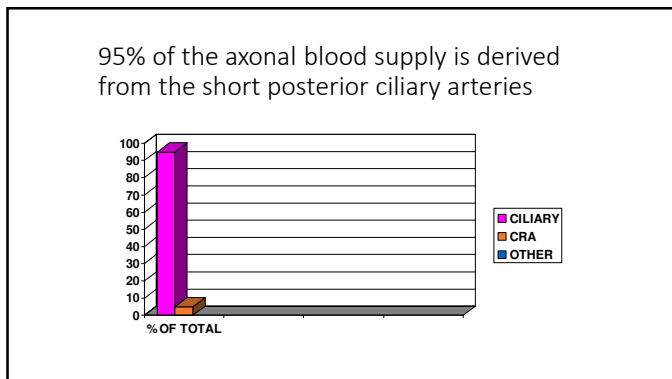
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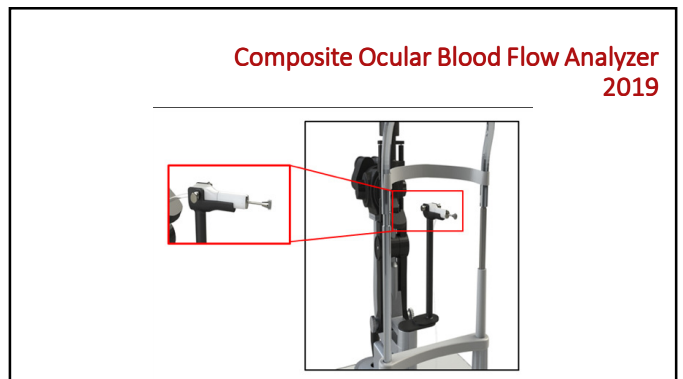
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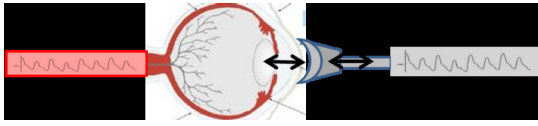


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Composite Ocular Blood Flow Analyzer 2019



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Dynamic Contour Tonometry Ocular Pulse Amplitude 2003



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The Clinical Utility of Dynamic Contour Tonometry and Ocular Pulse Amplitude
Weizer, Jennifer S. MD; Asrani, Sanjay MD; Stinnett, Sandra S. DrPH; Herndon, Leon W. MD
Journal of Glaucoma: December 2007 - Volume 16 - Issue 8 - pp 700-703



- Purpose: To determine if ocular pulse amplitude (OPA) as measured by dynamic contour tonometry (DCT) is related to severity of glaucoma...
- Conclusions: Increased OPA seems to correlate with less severe glaucoma and with increased CCT

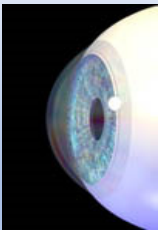
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Heidelberg
Doppler Flowmetry
(late 1990's)

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Myopia and Glaucoma



- Poor architecture-more vulnerable to IOP
- Eye size
- Low blood velocity in ophthalmic artery
- Low pulsatile ocular blood flow
- Low pulse amplitudes
- Challenge to perfusion

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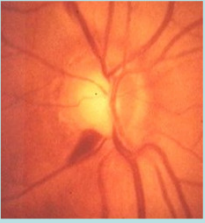
auto-regulation

The system which attempts to mitigate variations in intraocular pressure and systemic blood pressure to meet the metabolic requirements of the axonal bed.

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Drance Hemorrhage

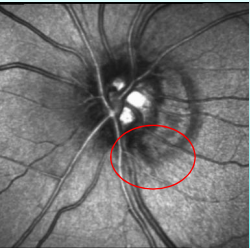
- 13% POAG / 20% NTG
- 84% are missed
- 100% with 2 disc hemorrhages will have field loss
- 81% with 1 disc hemorrhage will have field loss
- 3 fold progression risk – even under treatment



Liebmann et al

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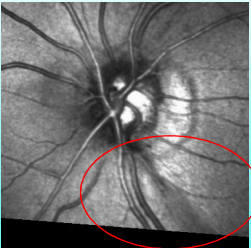
Drance Hemorrhage



BL: 6/4/2002 FUP #11: 11/14/2009 (89 months)
BL: 6/4/2002

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Drance Hemorrhage




BL: 6/4/2002 FUP #11: 11/14/2009 (89 months)
FUP #11: 11/14/2009 (88 months)

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Nocturnal Systemic Hypotension

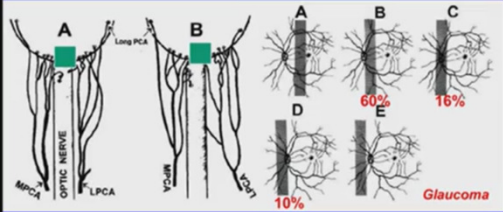
- Circadian cycle
- Beta blockers
- ACE inhibitors
- Anti-depressants
- Above Rx'd qhs
- Physical fitness



Suresh Singh Nayak
Professor of Ophthalmology
University of Iowa
Iowa City

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WSZ in the optic nerve - between SPCAs (paraoptic vessels)



10% 60% 16%
Glaucoma

Hayreh, IOVS 2004

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Nocturnal Systemic Hypotension Increases the Risk of Glaucoma Progression

Mary E. Charlson, MD, Carlos Gustavo de Moraes, MD, Alissa Link, MPH, Marin T. Wells, PhD, Gregory Harmon, MD, Janev S. Peterson, EdD, Robert Ritch, MD and Jeffrey M. Liebmann, MD
Ophthalmology, 2014 Oct; 121(10): 2004-2012


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.

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NTG: The Nocturnal Blood Pressure Factor Red Flags for Clinicians

- Postural hypotension
- Cold hands and feet
- Migraines
- Myopia
- Systemic beta blocker use



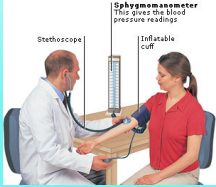
Carlos G. De Moraes, MD, New York City
Published 10 February 2014

Harper's Point Eye Associates

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Diastolic Perfusion Pressure (DPP)

- Diastolic Blood pressure – IOP = DPP
- Risk increases 6X below 55



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Progressing case despite controlled IOP (DPP=50 mmHg), cold hands (+)

Time	BP	IOP (OD) (Ta/Tp)	IOP (OS) (Ta/Tp)
10 am	109/65	14/15	14/15
M.D	106/68	13/15	13/14
2 pm	115/74	12/13	11/12
4 pm	113/77	11/12	12/12
6pm	102/62	13/14	13/13
8pm	96/61	11/13	11/13
10pm	105/64	12/14	12/14
M.N	96/61	11/13 (15) *	10/12 (14) *
3am	96/54	9/12 (15) *	9/12 (14) *
6am	97/54	10/11 (14) *	11/11 (13) *
8am	107/64	11/12	12/13

*nocturnal postural IOP

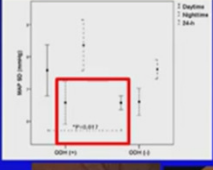
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Progressing patient with CAD & (+) antihypertensive medications

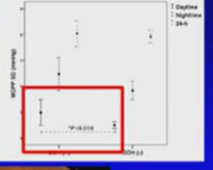
Time	BP	IOP (OD) (Ta/Tp)	IOP (OS) (Ta/Tp)
10am	129/85	14/15	14/15
M.D	126/78	15/16	15/16
2 pm	125/74	14/15	15/16
4 pm	133/77	13/15	14/15
6pm	122/72	11/16	16/17
8pm	126/81	13/15	13/14
10pm	125/74	15/16	14/15
M.N	103/59	14/15 (18) *	14/16 (17) *
3am	98/56	13/15 (18) *	14/15 (17) *
6am	97/60	13/14 (17) *	13/15 (16) *
8am	127/74	14/14	13/14

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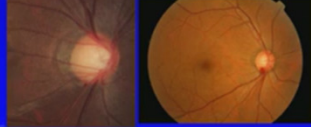
Nocturnal BP/OPP drop → Disc hemorrhages



BP (mmHg)



OPP (mmHg)



Kwon, Kook et al. AJO 2017

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When to consider OPP clinically?

- Progressing glaucoma despite well-controlled IOP
- Normal-tension glaucoma
- Patients with nocturnal hypotension
- History or symptoms of low BP, systemic antihypertensive medications, orthostasis
- Patients with optic disc hemorrhages

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Clinical Interventions to improve OPP

- Measure BP to identify those with low OPP
- Consider 24-h BP/IOP monitoring
- Modify systemic antihypertensive medication schedule or dose (pm → am, reduce dose to 1/2)
- Avoid topical beta-blockers for IOP reduction
- Reduce nocturnal IOP with topical PGAs or CAls
- Consider salty diet or salt tablets at night

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Macular Vessel Density and Ganglion Cell/Inner Plexiform Layer Thickness and Their Combinational Index Using Artificial Intelligence

Park, Keunheung, MD¹; Kim, Jinmi, PhD¹; Lee, Jiwoong, MD, PhD^{1,2}
Journal of Glaucoma: [September 2018 - Volume 27 - Issue 9 - p 750-760](#)

Conclusions: Macular vessel density was significantly decreased in glaucoma patients and showed an almost linear correlation with macular ganglion cell to inner plexiform layer thickness.

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Reduced Cerebral Blood Flow in the Visual Cortex and Its Correlation With Glaucomatous Structural Damage to the Retina in Patients With Mild to Moderate Primary Open-angle Glaucoma

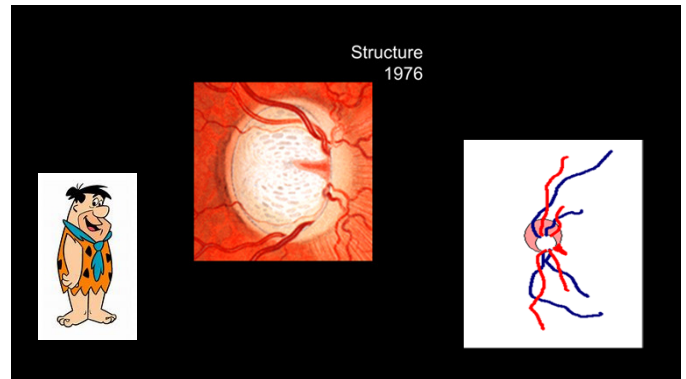
Wang, Qian, MD¹; Chen, Weiwei, PhD¹; Qu, Xiaoxia, PhD¹; Wang, Huaizhou, MD¹; Wang, Ying, MD¹; Zhang, Xun, MD¹; Li, Ting, MD¹; Wang, Ningli, MD, PhD¹; Xian, Junfang, MD, PhD¹
Journal of Glaucoma: [September 2018 - Volume 27 - Issue 9 - p 816-822](#)

Conclusions: The complex pathologic progress of POAG includes abnormal cerebral perfusion within the visual cortex in mild to moderate disease stages. The association of cerebral perfusion changes with alterations of the optic disc and the retina may contribute to the early diagnosis of POAG.

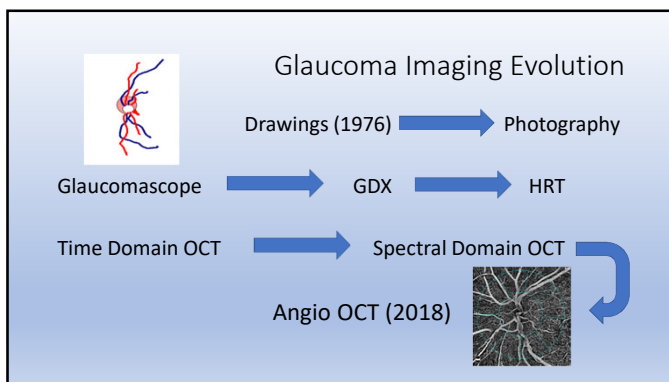
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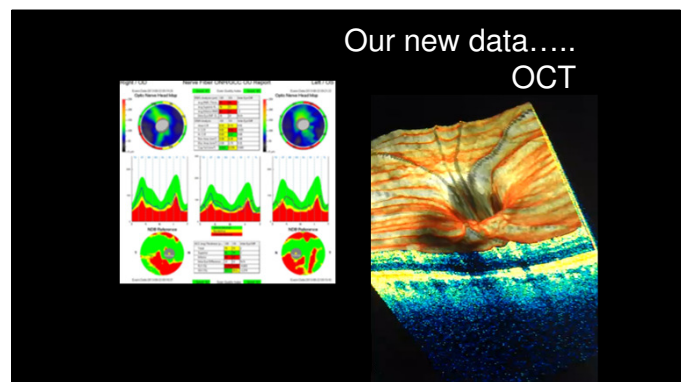
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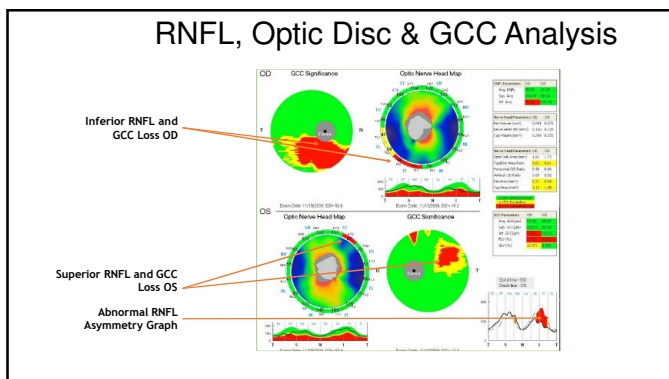
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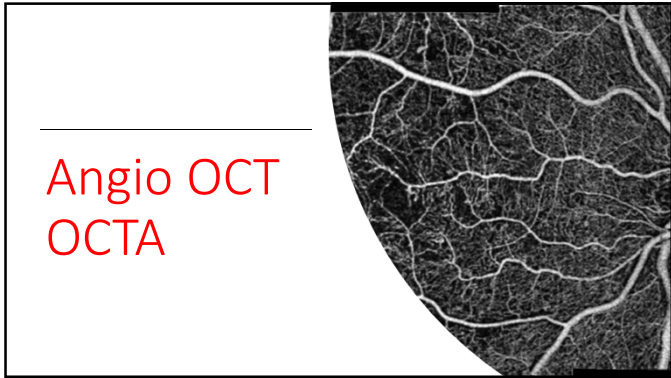


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OCT best for early and moderate disease

- Plasticity of fields with early loss
- OCT "Floor Effect" at about 50 microns

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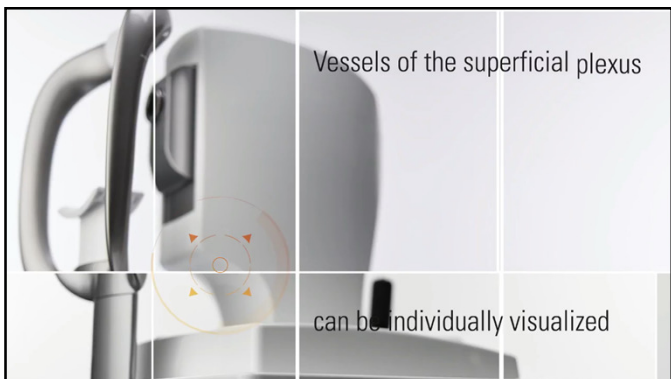
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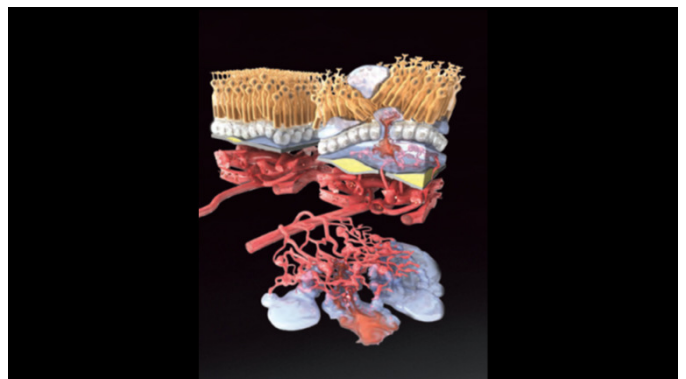
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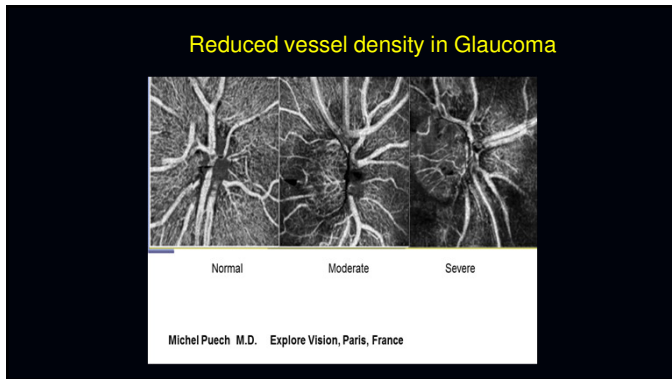
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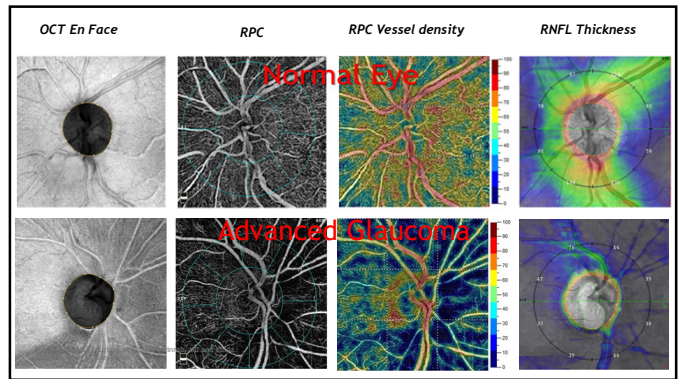
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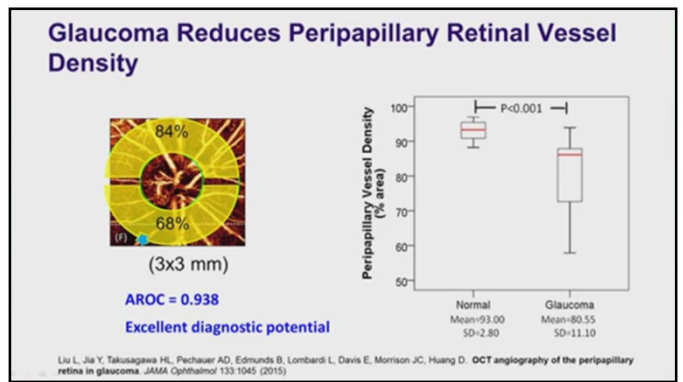
7th WORLD GLAUCOMA CONGRESS
JUNE 28 - JULY 1, 2017 HELSINKI

OCT Angiography in Glaucoma

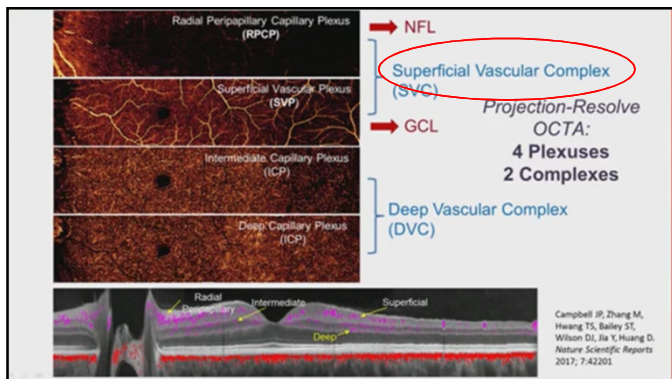
David Huang, MD, PhD
Peterson Professor of Ophthalmology
Professor of Biomedical Engineering
Casey Eye Institute, Oregon Health & Science University
Portland, Oregon

7th WORLD GLAUCOMA CONGRESS

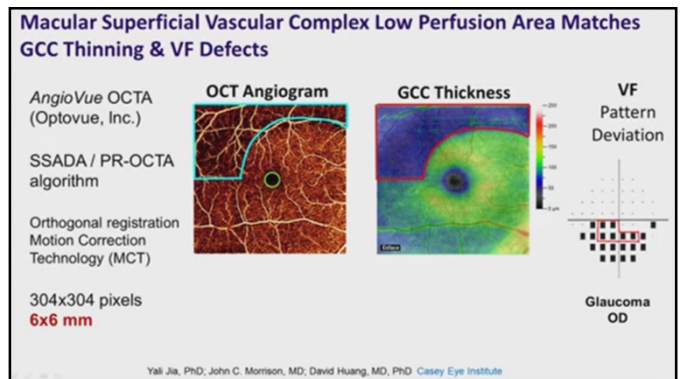
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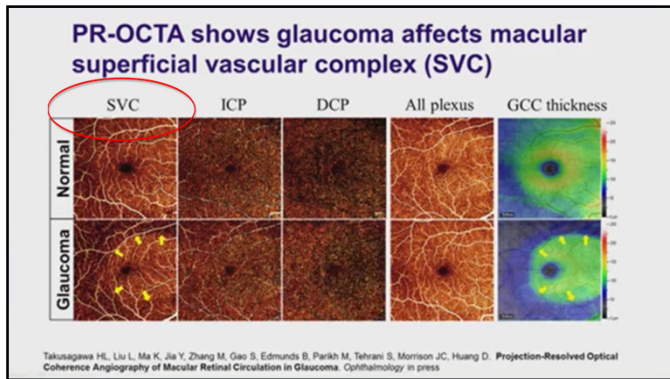
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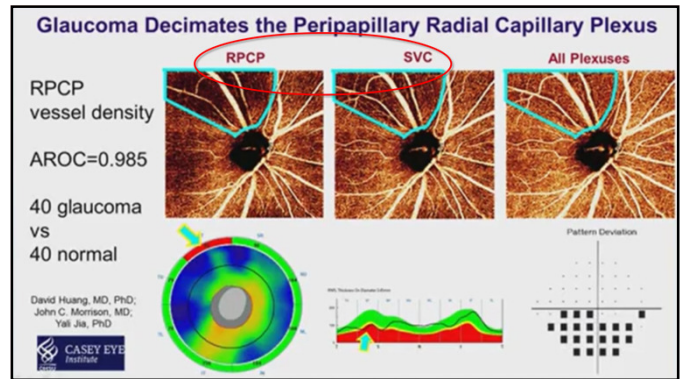
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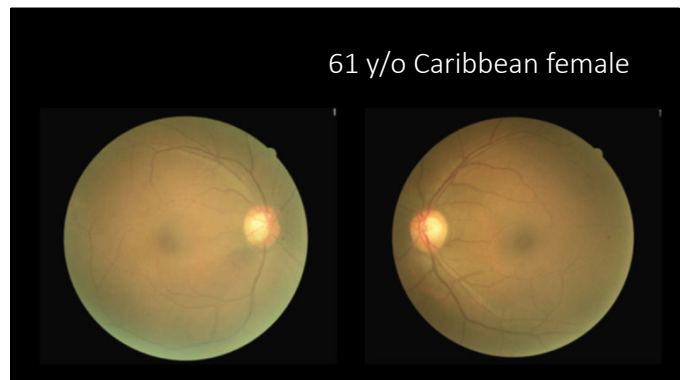


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Decreased Vessel Density cause or effect?

- Theory 1**
Axonal loss causes reduced demand of blood (ie. decrease in VEG-F), so vessels recede as the result of decrease in signal.
- Theory 2**
Axonal loss secondary to acute or chronic ischemia

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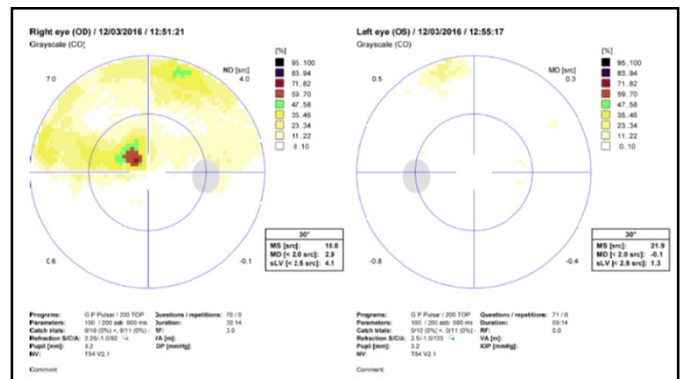


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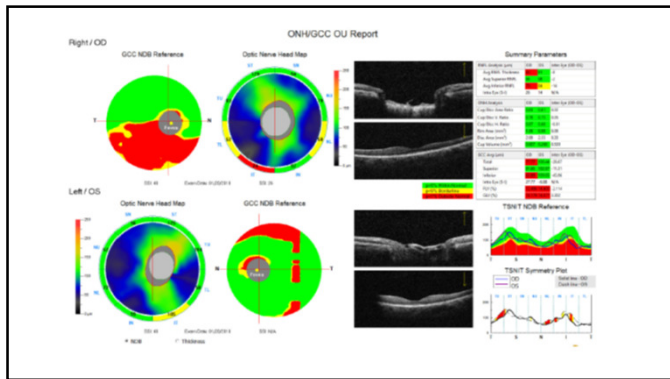
history

- Positive family glaucoma History
- 5 years treatment latanoprost monotherapy
- IOP's with medication 20 mm OU
- OD loss approaching fixation
- OD wedge NFL defect

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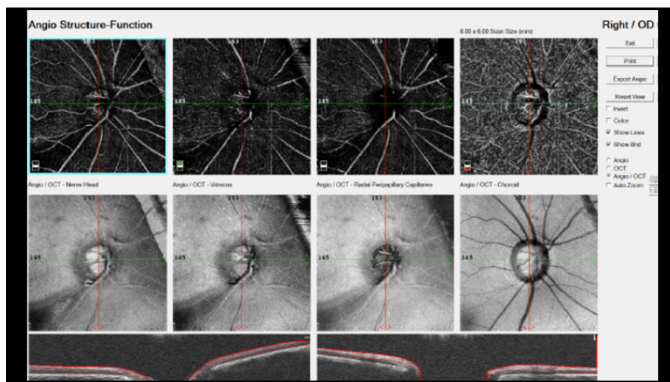
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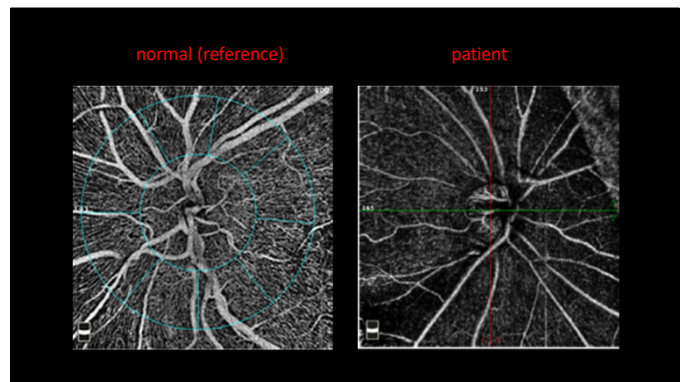
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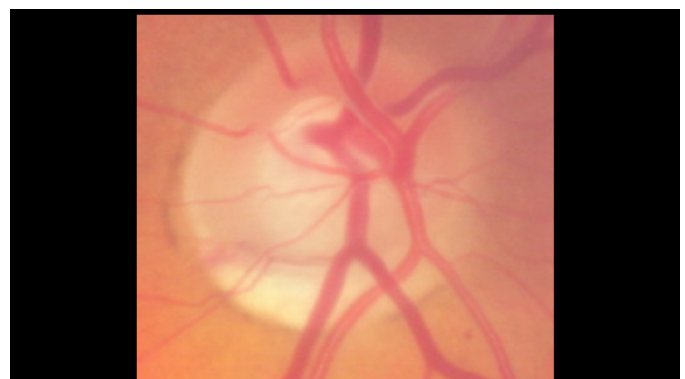
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76 y/o Caucasian female

- Chronic Drance hemorrhage
- 4 topical medicines
- Superior and paracentral field loss
- "controlled" IOP's in high teens

Detailed description: This slide contains a list of clinical findings for a 76-year-old Caucasian female. The findings include chronic Drance hemorrhage, use of 4 topical medicines, superior and paracentral field loss, and 'controlled' IOP's in high teens. A small, low-resolution image of retinal vasculature is shown in the bottom right corner.

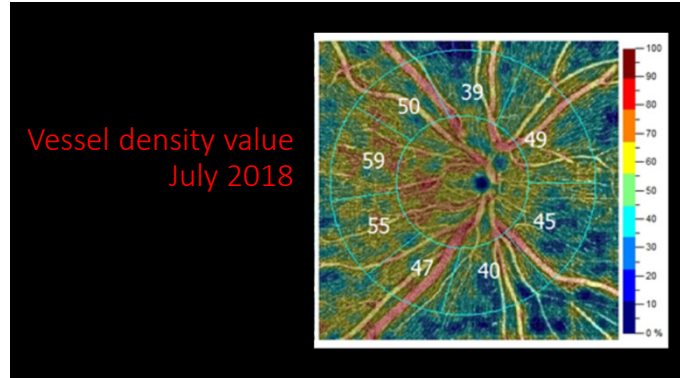
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73




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Choroidal Microvascular Dropout in Primary Open-angle Glaucoma Eyes With Disc Hemorrhage

Rao, Harsha L, MD, PhD¹; Sreenivasalah, Shruthi, DNB²; Dixit, Shivani, MD³; Riyazuddin, Mohammed, BOpt⁴; Dasari, Sriakshmi, BOpt⁵; Venugopal, Jayasree P, MD⁶; Pradhan, Zia S, DNB, FRCOphth⁷; Puttaiah, Narendra K, DNB⁸; Devi, Sathi, MD⁹; Mansouri, Kaweh, MD¹⁰; Webers, Carroll A.B., MD, PhD¹¹; Weisenb, Robert N., MD¹²
Journal of Glaucoma: [March 2019 - Volume 28 - Issue 3 - p 181-187](#)

Conclusions: Prevalence of choroidal microvascular dropout was significantly greater in POAG eyes with Drance Hemorrhage compared with POAG eyes without hemorrhage.

Choroidal microvascular dropout in POAG eyes was also significantly associated with central VF defects and greater severity of glaucomatous damage.




75

Optical Coherence Tomography Angiography of Optic Disc in Eyes With Primary Open-angle Glaucoma and Normal-tension Glaucoma

Toshev, Anani P, MD¹; Schuster, Alexander Karl-Georg, MD, MSc²; ul Hassan, Shahzada N, MD³; Pfeiffer, Norbert, MD⁴; Hoffmann, Esther M, MD⁵
Journal of Glaucoma: [March 2019 - Volume 28 - Issue 3 - p 243-251](#)

Conclusions: Overall, glaucomatous eyes had lower peripapillary Vessel Density compared with normal and OHT eyes. There is a strong relationship between the peripapillary structure of RNFL and its vasculature.

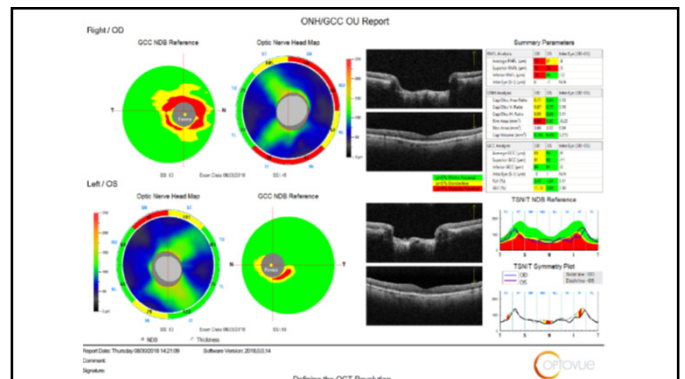


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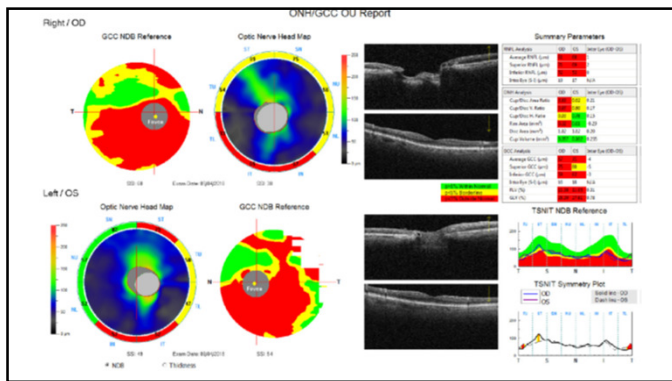
75 year old
Caucasian female

- Family history
- 3 medicines

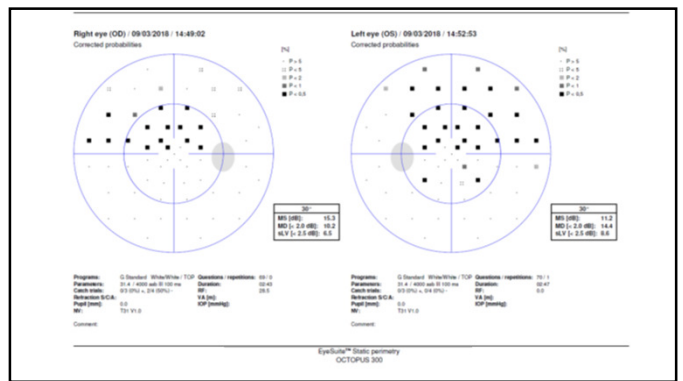
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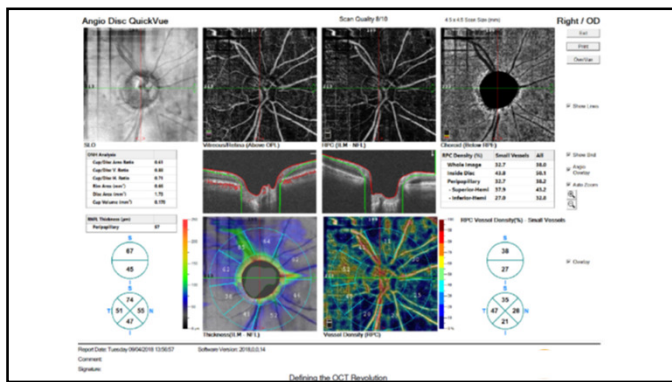
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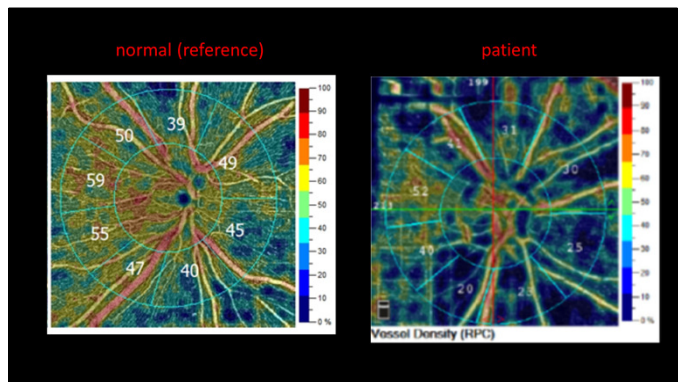
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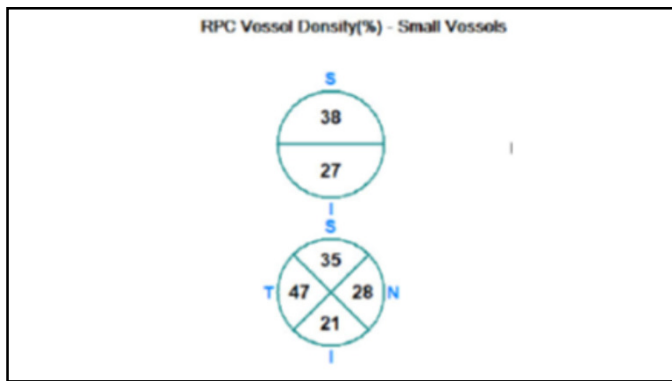
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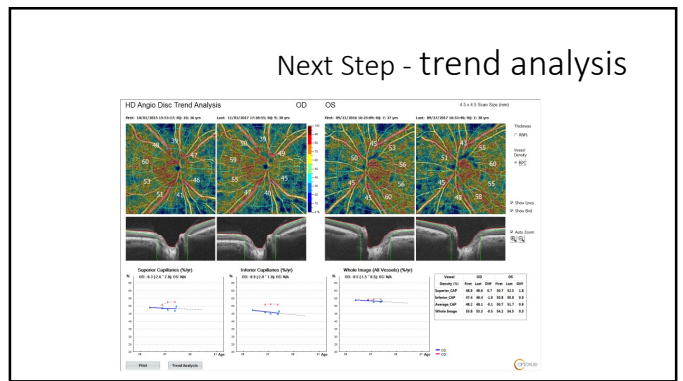
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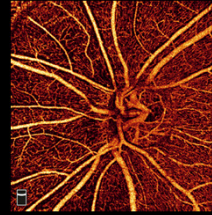
90

NO Donators

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%

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Now that we can measure it,
how can we change it?



92

Decrease IOP significantly

- Small changes in IOP seldom alter blood flow significantly because of the mitigating effect of autoregulation
- Dramatic IOP decreases overwhelm autoregulation and increase ocular perfusion

93

Calculate Diastolic Perfusion Pressure

- Be more aggressive in treating individuals with DPP below 55



94

Look for over treatment of high blood pressure

- Avoid night time systemic beta blockers
- Communicate with prescribing MD's to share your concern

95

Counsel hydration / salt intake / lifestyle

- Encourage electrolyte drinks
- Encourage hydration at bedtime
- Consider salt tablets at bedtime
- Encourage self monitoring of blood pressure

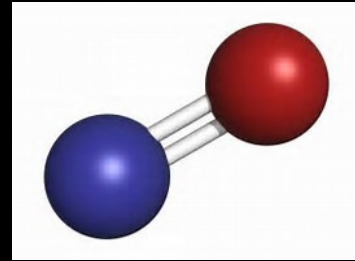


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Consider topical medications which may augment blood flow

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Nitric Oxide (NO)



98

Nitric Oxide in Medicine

- Nitroglycerin discovered by the Italian chemist Ascanio Sobrero
- Ascanio also noted that it relieved headaches
- Alfred Nobel – experimented with nitroglycerine and developed dynamite
- Lauder Brunton, a distinguished British physician, had found in 1867 that organic nitrates were effective in relieving pains in angina pectoris
- Alfred Nobel established the prizes in 1895



99

NO in non-ocular pathophysiology

- eNOS reduces production of NO which then reduces the production of cGMP.
- cGMP dysregulation plays a role in many human disease process related to vasoconstriction and / or vasospasm

100

NO in non-ocular pathophysiology

- Angina pectoris
- Pulmonary hypertension
- Erectile dysfunction
- Thrombosis
- Atherosclerosis

101

Increasing cGMP levels treats

- Erectile dysfunction
- Asthma
- Pulmonary arterial hypertension
- Myocardial failure
- Endotoxic shock

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**new and now available
Vyzulta
(Latanoprostene Bunod)**



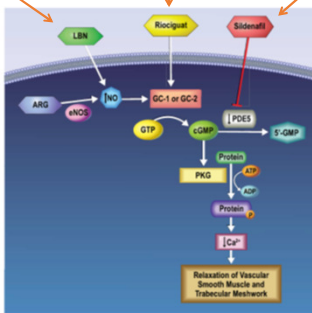
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**Bausch & Lomb / Nicox
latanoprostene bunod
VYZULTA**

- Preclinical studies have shown that NO plays a role in controlling IOP in normal eyes by increasing aqueous humor outflow through the trabecular meshwork and Schlemm's canal.
- Studies have also demonstrated that patients with glaucoma have reduced levels of NO signaling in their eyes, providing a rationale for the therapeutic value of NO-releasing molecules for patients with open-angle glaucoma or ocular hypertension.

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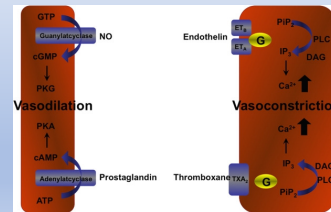
Glaucoma Pulmonary Hypertension Erectile Dysfunction



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Nitric Oxide (NO) in the optic nerve

- NO donors decrease vascular resistance by relaxing smooth muscle



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Latanoprostene Bunod 0.024% in Subjects With Open-angle Glaucoma or Ocular Hypertension: Pooled Phase 3 Study Findings

Weinreb, Robert N. MD; Liebmman, Jeffrey M. MD; Martin, Keith R. MD; Kaufman, Paul L. MD; Vittitow, Jason L. PhD
Journal of Glaucoma: January 2018 - Volume 27 - Issue 1 - p 7-15

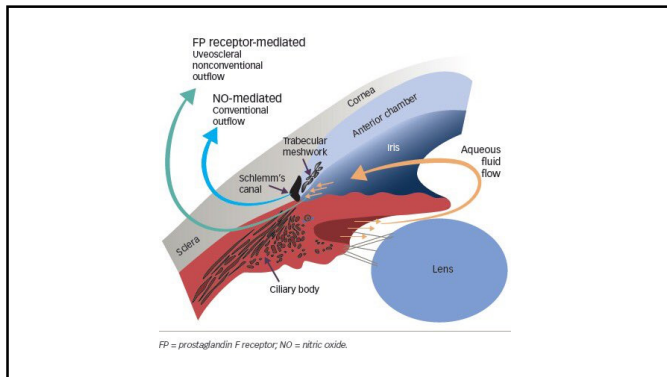
Conclusions: In this pooled analysis of subjects with OAG and OHT, LBN 0.024% qd provided greater IOP-lowering compared with timolol 0.5% bid and maintained lowered IOP through 12 months. LBN demonstrated a safety profile comparable to that of prostaglandin analogs.

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**Bausch & Lomb / Nicox - latanoprostene bunod
"VYZULTA"**

- Showed greater IOP reduction compared with latanoprost, with the differences reaching 1.23 mm Hg
- 52-Week Safety Study: VYZULTA™ Reduced Mean IOP to 14.4 mm Hg in Subjects with Mean Low Baseline IOP of 19.6 mm Hg

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Latanoprostene Bunod

- Reduces trabecular meshwork cell contractility and increases outflow compared with latanoprost
- May increase blood flow to the axonal bed

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Nitric Oxide Pipeline

- Bimatoprost + NO donator
- CAI + NO donator

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Rhopressa

(netarsudil ophthalmic solution .02%)
Aerie Pharmaceuticals, Inc.

(approved 2018)

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Rhopressa

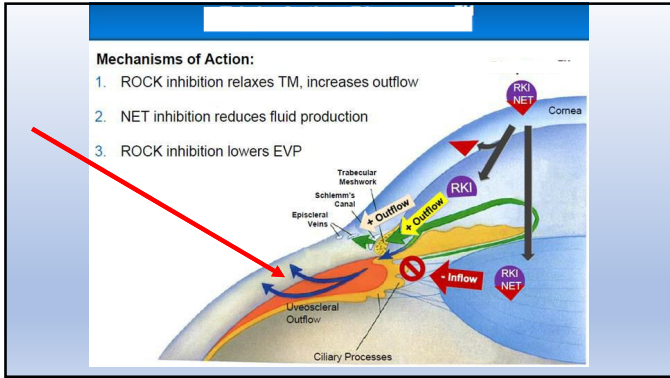
(netarsudil ophthalmic solution .02%)

- Rho kinase inhibition ("ROCK" inhibitor)
- QD dosing
- Complimentary to prostaglandins
- Reduction of epi scleral venous pressure
- Maybe, enough IOP reduction to override autoregulation

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- Patients treated with once-daily Rhopressa experienced a reduction of IOP ranging from 3.9 mmHg to 4.1 mmHg⁴
- Patients treated with twice-daily timolol experienced a reduction of IOP ranging from 3.5 mmHg to 4.6 mmHg

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INTRO SAFETY EFFICACY COMMERCIAL COMPETITIVE LANDSCAPE RISK VALUATION

In ROCKET1 and ROCKET2, somewhere between 5% and 15% of patients encountered one or more of the following side effects

Corneal deposits

Blurry vision

Conjunctival hemorrhage

Wunderkind Research

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**NEW
Rocklatan**

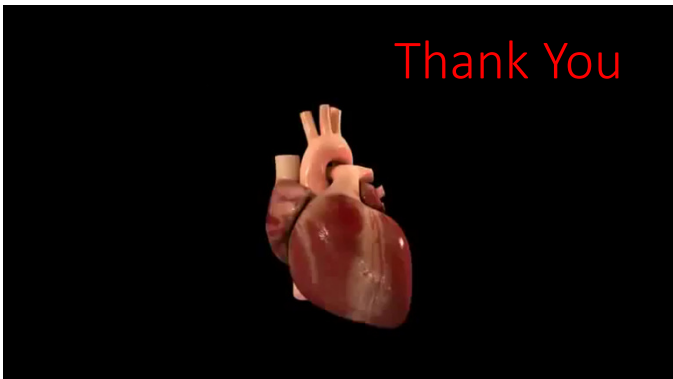
rho kinase inhibitor + PGA
(approved 3/12/2019)

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Rhopressa™ and Roclatan™ Potential Product Advantages

<p>Rhopressa™ Positioning</p> <p>Potential drug of choice as adjunctive therapy to PGAs when additional IOP lowering is desired</p>	<p>Roclatan™ Positioning</p> <p>Potential drug of choice for patients requiring maximal IOP lowering</p>
<p>Rhopressa™ Advantages</p> <ul style="list-style-type: none"> • Efficacy vs. other adjunctive therapies • QD PM dose • Lack of serious and systemic drug-related AE's 	<p>Roclatan™ Advantages</p> <ul style="list-style-type: none"> • Efficacy vs. all other glaucoma therapies • QD PM dose • Lack of serious and systemic product-related AE's

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