

Ocular Blood Flow and Glaucoma - 2018

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Glaucoma and Diabetes Eye Institute

Cincinnati, Ohio

Financial Interests

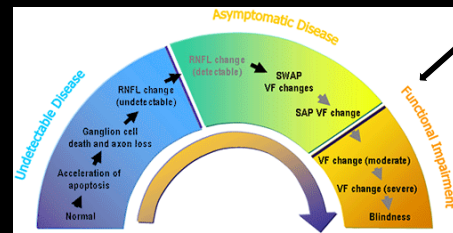
- Alcon
- Optovue
- Reichert
- Haag-Streit

"The excavation of the disc in glaucoma is not a purely mechanical result of exalted pressure; it is, in part at least, an atrophic condition which, though primarily due to pressure, includes vascular changes and impaired nutrition of the substance of the optic disc... which may possibly progress even though all excessive pressure be removed".

Priestly Smith, 1885

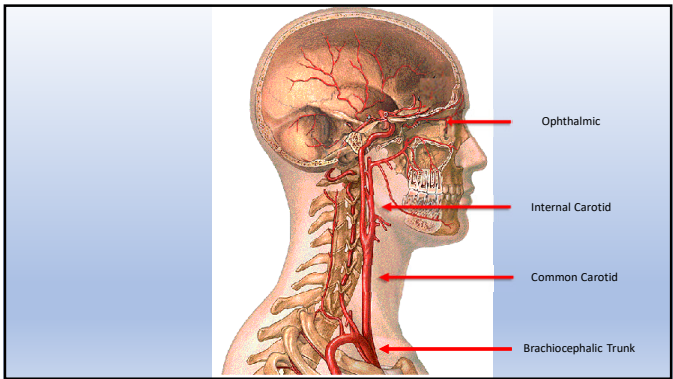
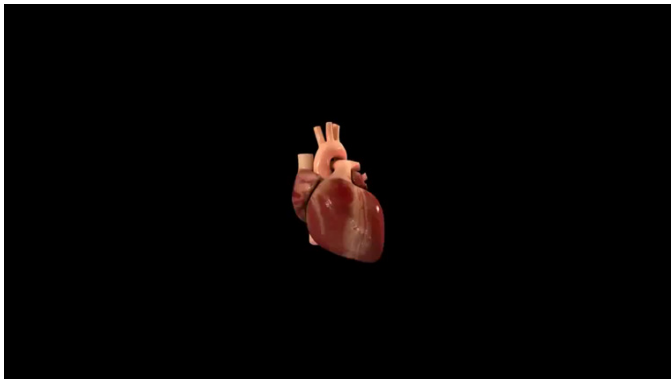
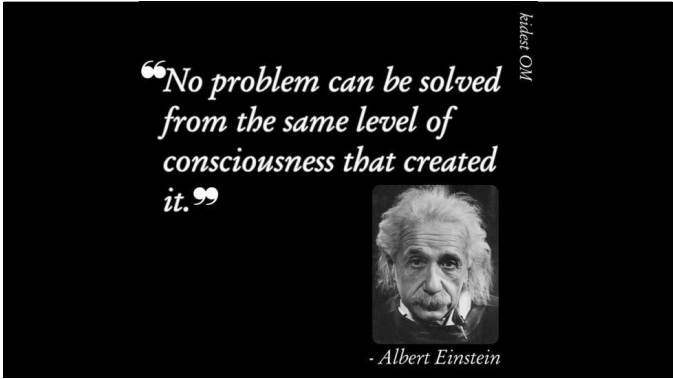
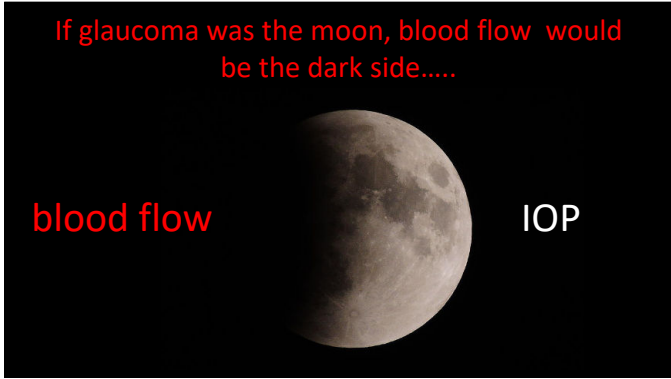


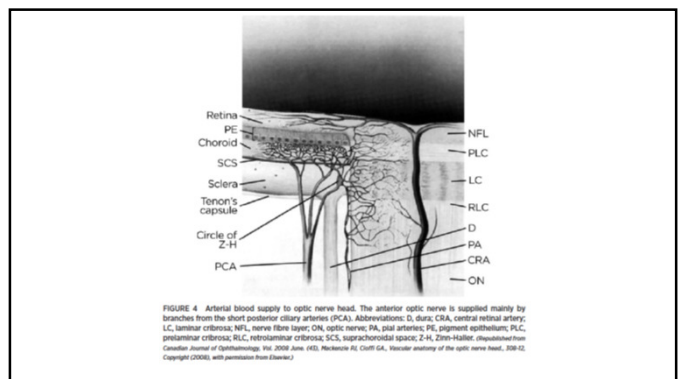
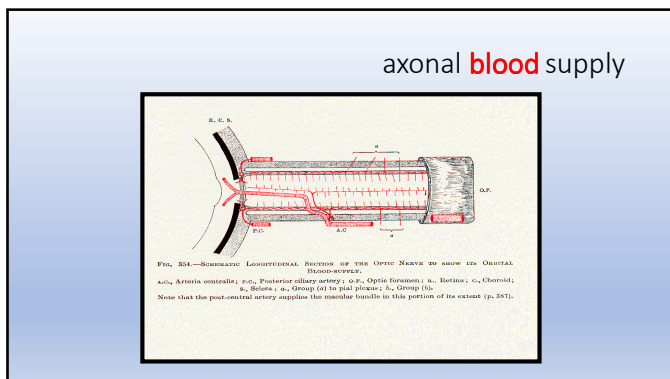
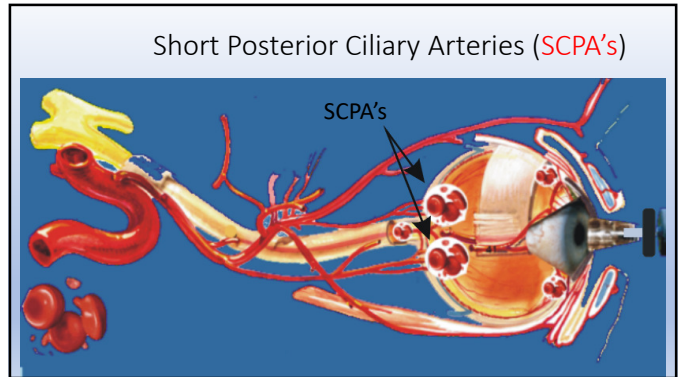
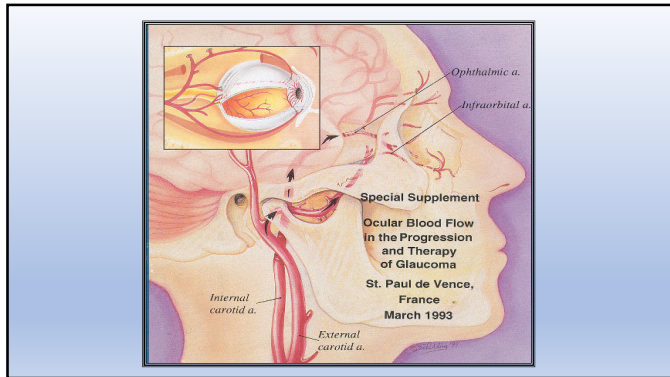
glaucoma continuum

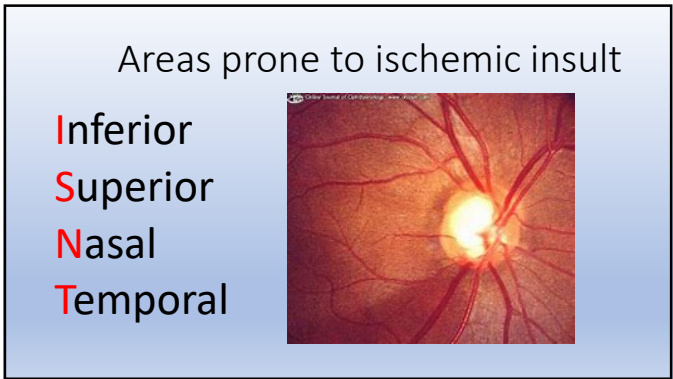
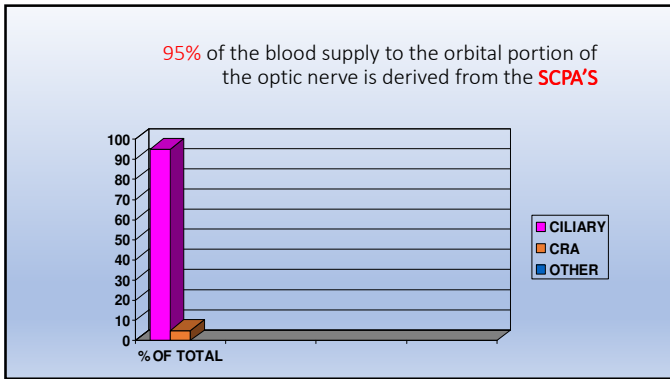
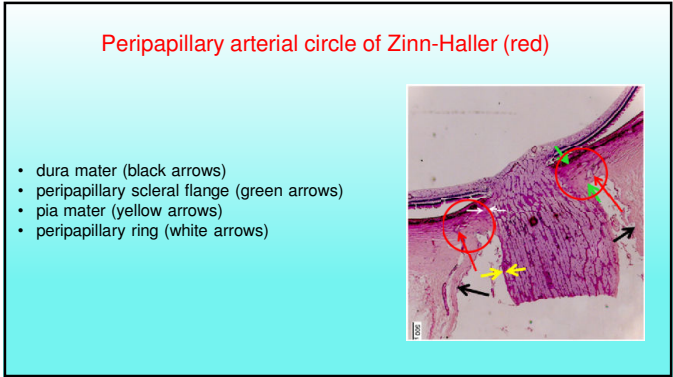
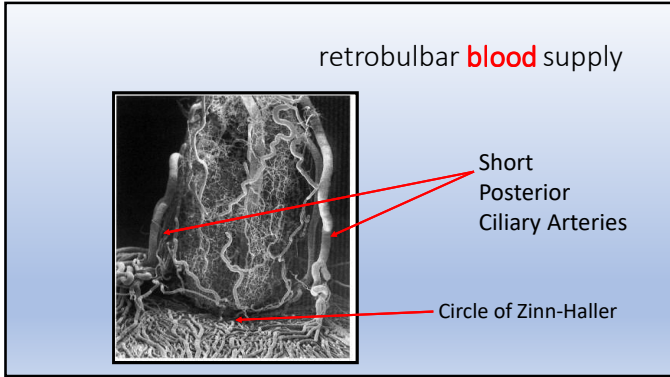


Adapted from Weinreb et al. Am J Ophthalmology. 2004;138:458-467.

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Vascular Factors in Glaucoma

- Cardiovascular deficiencies / low blood pressure
- Physical limitations of vascular architecture
- IOP induced hypo perfusion
- Vasospasm
- Nocturnal systemic hypotensive episodes
- Limitations of autoregulation

Autoregulation

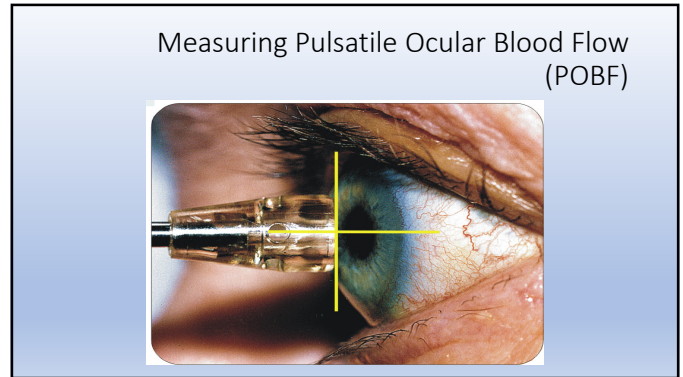
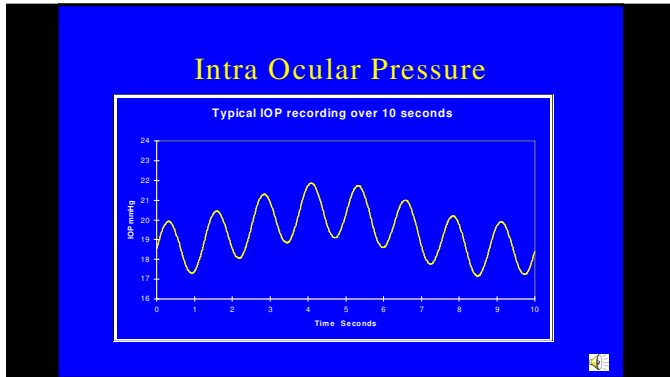
The system which attempts to mitigate variations in intraocular pressure and systemic blood pressure to fulfill ongoing axonal metabolic requirements.

Ocular Auto-regulatory Defects ?

- Aging?
- Heredity?
- Acquired?
- Possible over action of Endothelin-1
- Possible under action of Nitric Oxide
- Vasospasm or migraine

Paradigm Ocular Blood Flow Analyzer
1990's





History of Pulsatile Ocular Blood Flow Analysis

Maurice Langham, David Massey (OBF Labs, U.K.) - mid 1980's

Malcolm Redman, David M, Silver, PhD (OBF Labs, U.K.) – mid 1990's

David M, Silver, PhD (Paradigm Medical, Salt Lake City) - 1995 - 2003

POBF and Normal Tension Glaucoma

- 236 patients with NTG and 109 with suspicious discs compared to 777 normal controls. (1998 Investigative Ophthalmology – R. A. Hitchings, Moorfields Eye Hospital)
- Conclusion: Suspicious optic disc parameters that correlate with low POBF may be a marker for glaucoma

Measuring Ocular Pulse Amplitude (OPA)



Pascal
Dynamic Contour
tonometry
2003 - present



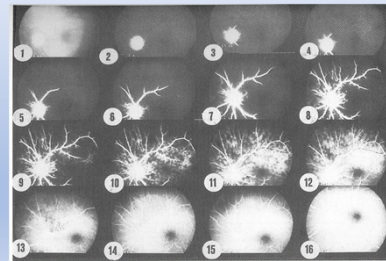
The Clinical Utility of Dynamic Contour
Tonometry and Ocular Pulse Amplitude

Weizer, Jennifer S. MD*¹; Asrani, Sanjay MD*; Stinnett, Sandra S. DPHM; Herndon, Leon W. MD*
Journal of Glaucoma: December 2007 - Volume 16 - Issue 8 - pp 700-703
doi: 10.1097/IJG.0b013e31806a294e

- 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



Indocyanine Green
Perfusion Pressure Video Angiography

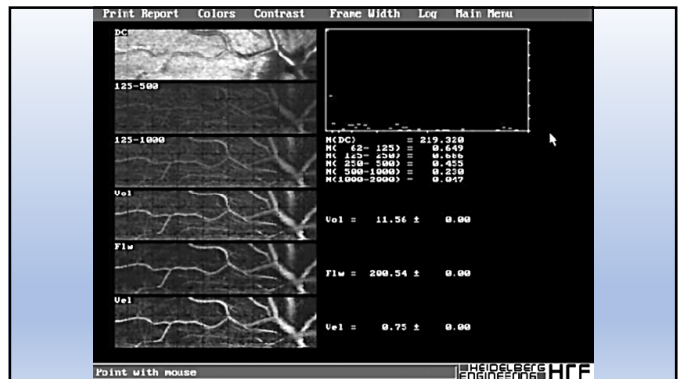


Watershed Zones

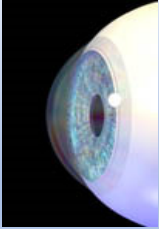
- The Circle of Zinn-Haller provides the significant source of blood to the orbital portion of optic nerve axons.
- The architecture of the Circle of Zinn-Haller or damage to that area can leave certain areas poorly perfused and, thereby, more prone to ischemic insult.



Heidelberg Doppler Flowmetry (late 1990's)



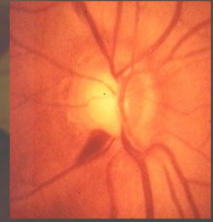
Myopia and Glaucoma



- 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

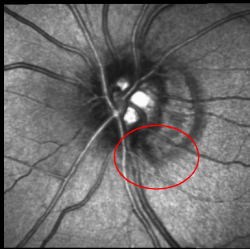
Drance Hemorrhage

- 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



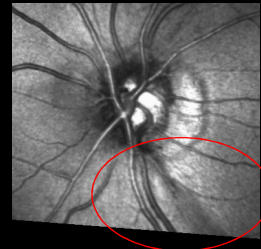
Liebmann et al

Drance Hemorrhage



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

Drance Hemorrhage



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

IOP and Blood flow are
like fraternal twins
in glaucoma risk



Nocturnal Systemic Hypotension

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



Suman Singh Nayak
Professor of Ophthalmology
University of Iowa
Iowa City

Nocturnal Systemic Hypotension Increases the Risk of Glaucoma Progression

Mary E. Charlson, MD, Carlos Gustavo de Moraes, MD, Alissa Link, MPH, ~~Manjit K. Walle, PhD, Gregory Hamron MD, Janey C. Peterson, EdD, Robert Ritch, MD, and Jeffrey M. Liebmann, MD~~
Ophthalmology, 2014 Oct; 12(11): 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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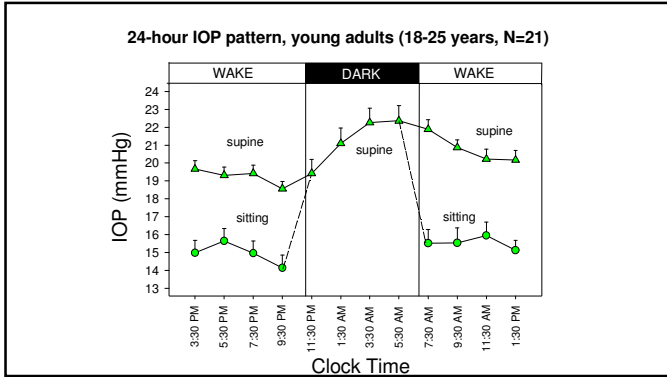
NTG: The Nocturnal Blood Pressure Factor Red Flags for Clinicians

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



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

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Diastolic Perfusion Pressure (DPP)

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

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Perfusion and Progression: Studies

- Baltimore Eye Survey – 6X excess of POAG in lowest category of Perfusion
- Egna-Newmarket Study – Lower Diastolic Perfusion Pressure associated with increase frequency of POAG
- Barbados Eye Study – Increased 4 year risk of POAG at lower perfusion pressure
- Proyecto Ver Study – Increased POAG with lower diastolic perfusion pressure

Classification of Blood Pressure - 2018:

Four new BP categories based on the average of two or more in-office readings.

- Normal: < 120 mm Hg Systolic BP and < 80 mm Hg Diastolic BP
- Elevated: 120-129 mm Hg SBP and < 80 mm Hg DBP
- Stage 1 Hypertension: 130-139 mm Hg SBP or 80-89 mm Hg DBP and
- Stage 2 Hypertension: ≥ 140 mm Hg SBP or ≥ 90 mm Hg DBP

Body Mass Index and NTG

78,777 women studied

Conclusions: Each unit increase in body mass index (BMI) was associated with a 6% lowered risk for normal-tension glaucoma

Louis R. Pasquale, MD

Director of the Glaucoma Service - Massachusetts Eye and Ear Infirmary

Fit but Fainting – Runners World

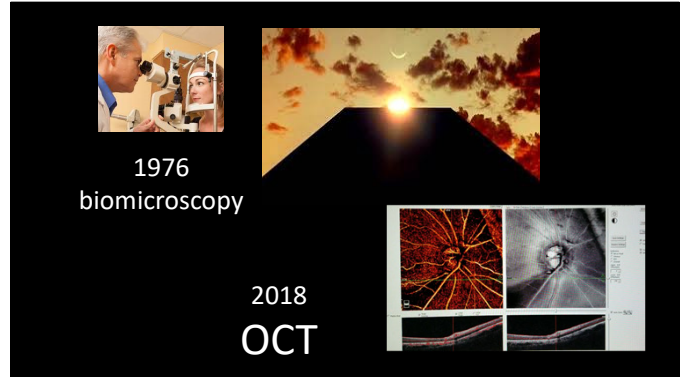


Transformation....



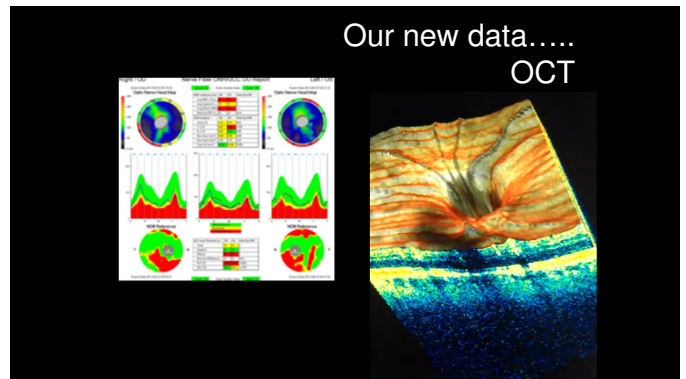
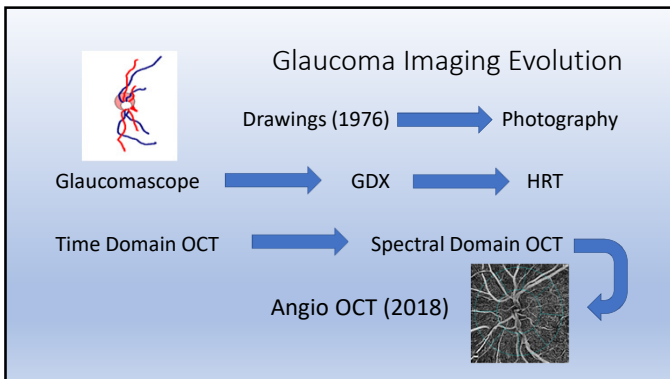
Harper / Paint Eye / iStockphoto



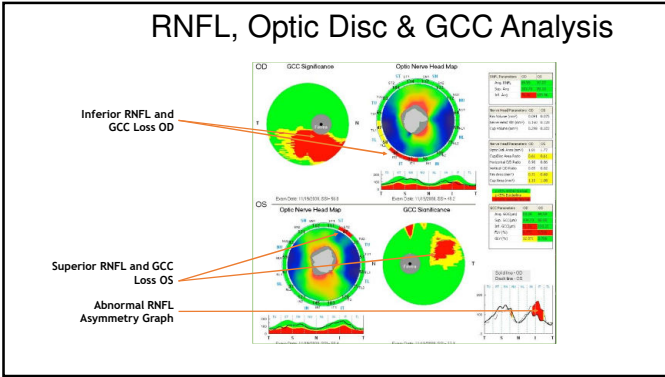


1976
biomicroscopy

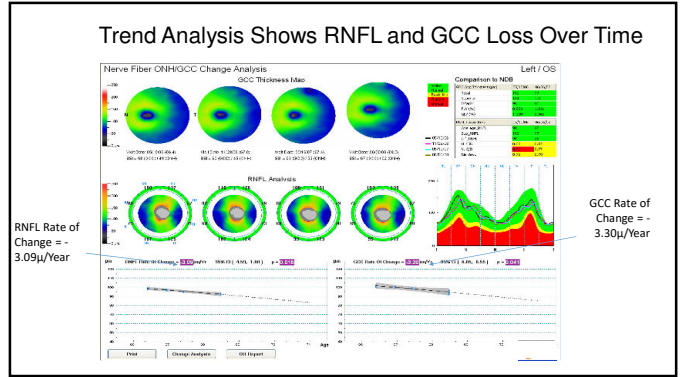
2018
OCT



RNFL, Optic Disc & GCC Analysis



Trend Analysis Shows RNFL and GCC Loss Over Time



OCT best for early and moderate disease

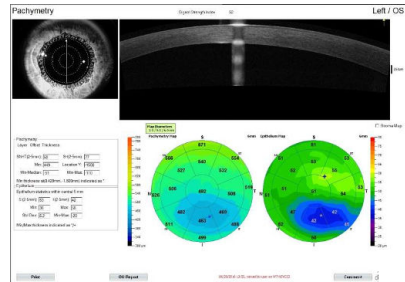
- Plasticity of fields with early loss
- OCT "Floor Effect" at about 50 microns

OCT perks

Angle Measurement with Quantification



OCT measuring Corneal thickness



Angio OCT
OCTA



SS OCT Angio™
TOPCON

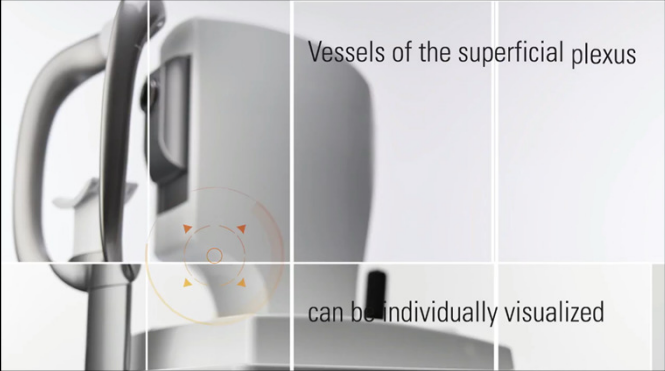
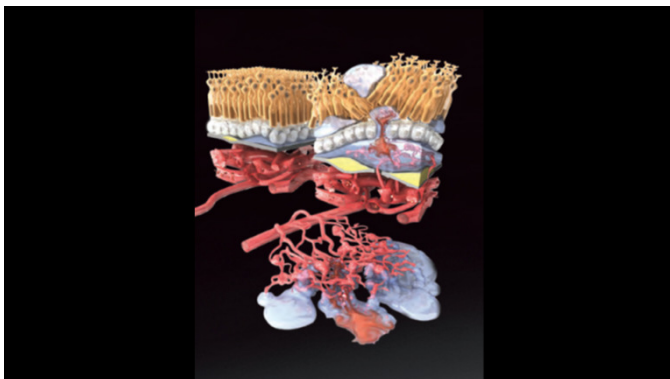
Not available in U.S.



Harper's Point Eye Resolutions

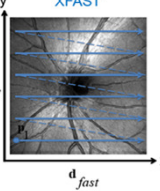
Vessels of the superficial plexus

can be individually visualized

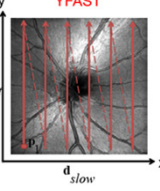
How Does MCT Work?

XFAST



d_{slow} (y-axis), d_{fast} (x-axis)

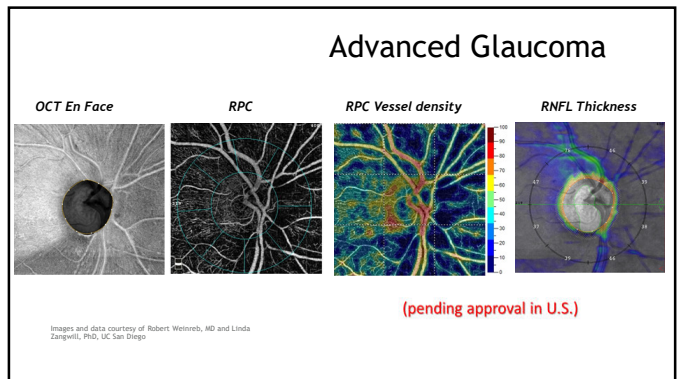
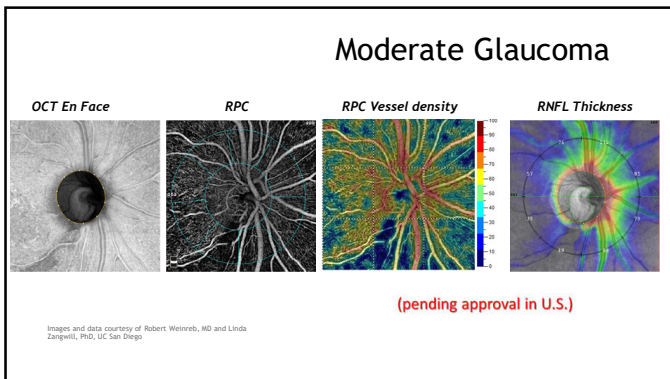
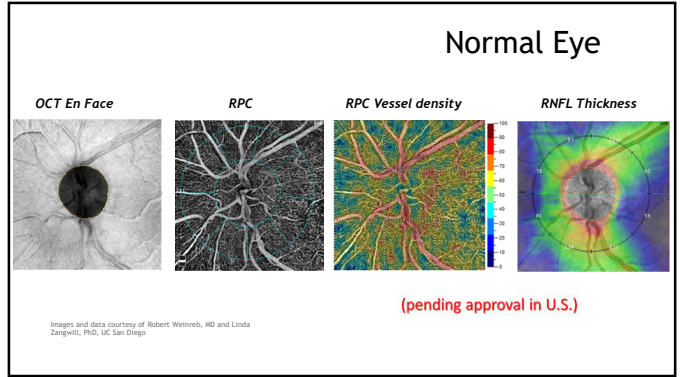
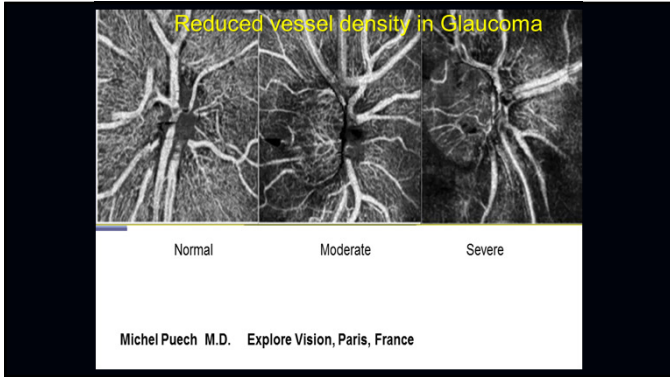
YFAST



d_{fast} (y-axis), d_{slow} (x-axis)

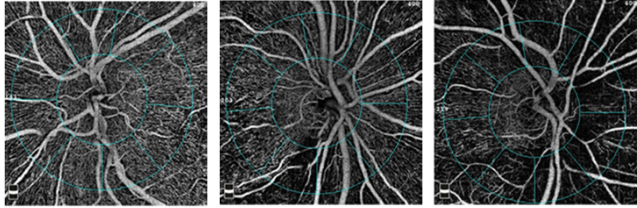
3D based pixel-level registration and averaging removes motion artifacts (lateral and z-motion) and improves image quality.

Kraus M., Pitsaad B., et al., Motion Correction in Optical Coherence Tomography Volumes on a per A-scan Basis using Orthogonal Scan Patterns. Biomedical Optics Express 2012, 3:1162.



loss of peripapillary vasculature

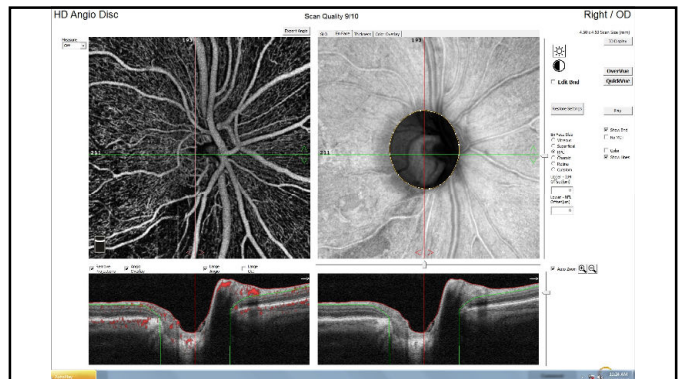
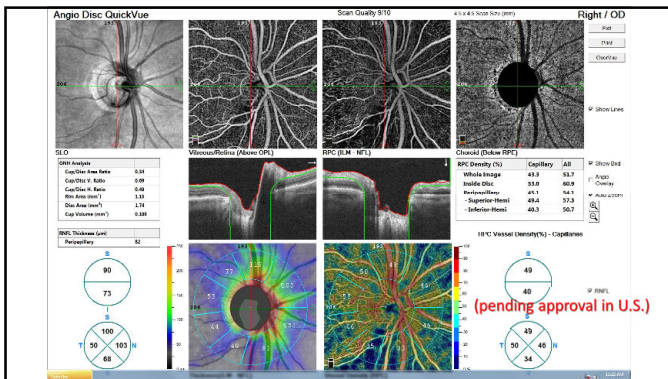
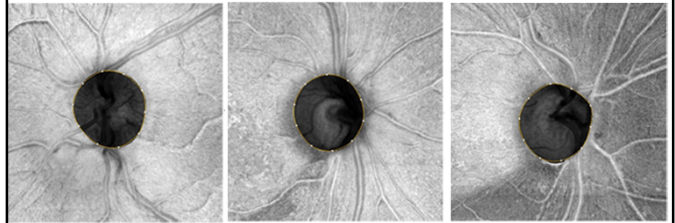
normal moderate advanced



OCT En Face Normal

OCT En Face Moderate

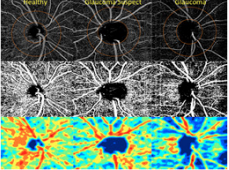
OCT En Face Advanced



ARVO JOURNALS

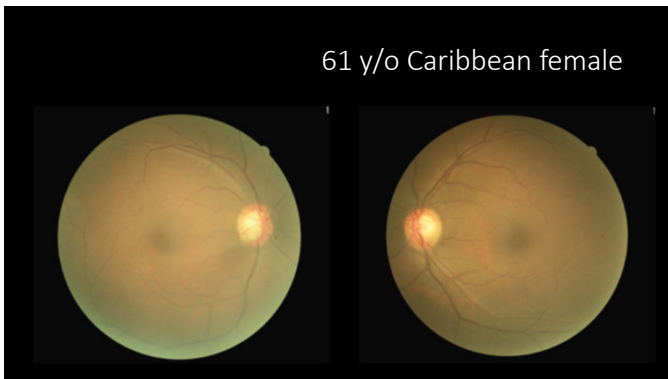
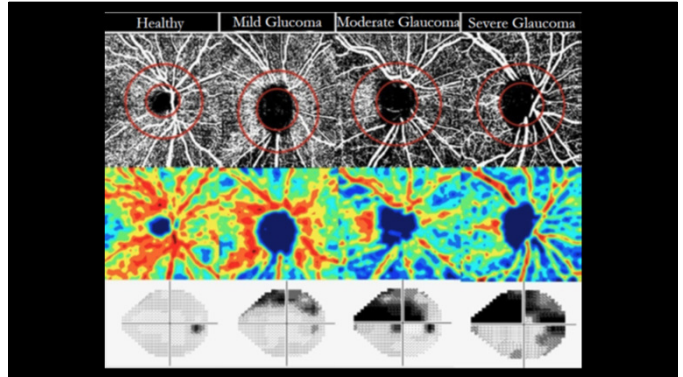
From: Optical Coherence Tomography Angiography Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes
 Invest. Ophthalmol. Vis. Sci. 2016;57(8):OCT451-OCT459. doi:10.1167/iov.15-18944

Adeleh Yarmohammadi; Linda M. Zangwill; Alberto Diniz-Filho; Min Hee Suh; Patricia Isabel Manalastas; Naem Falehee; Siamak Yousefi; Akram Belghith; Luke J. Saunders; Felipe A. Medeiros; David Huang; Robert N. Weinreb




Retinal nerve fiber layer vessel density map in healthy, glaucoma suspect, and open-angle glaucoma eyes. Top row: circumpapillary vessel density map measurement region defined. Middle row: vessel density extracted map overlay on the major retinal vessels. Bottom row: area vessel density color-coded map.

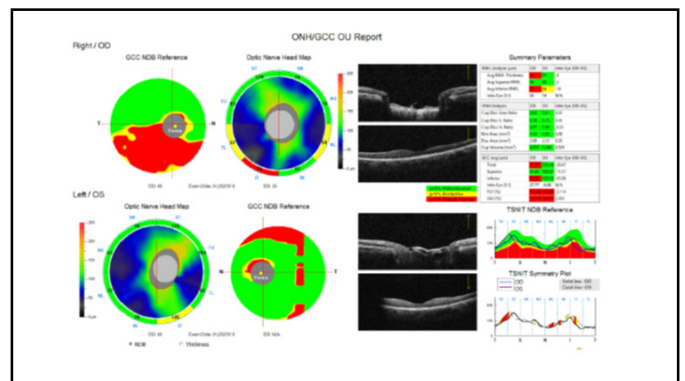
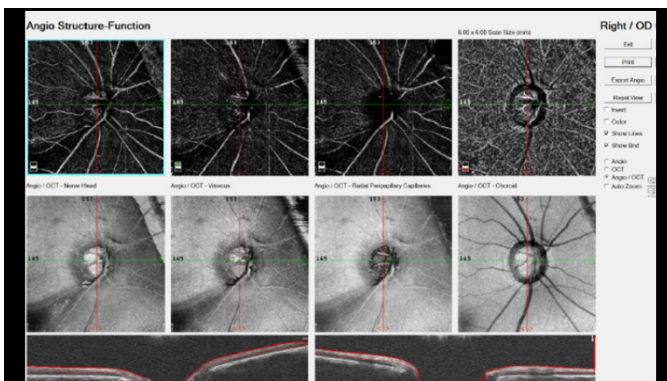
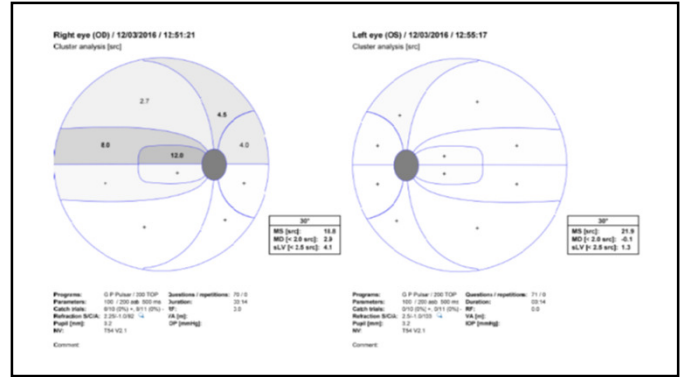
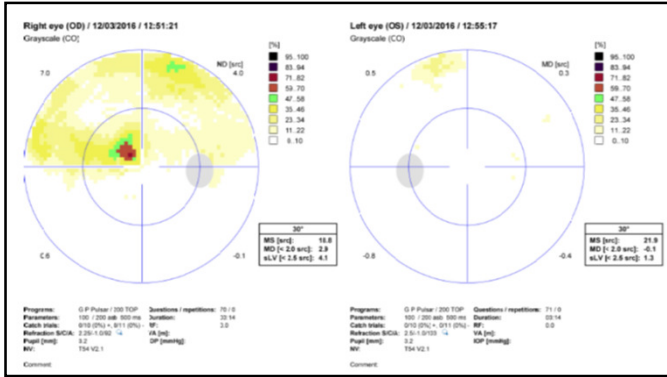
Date of download: 12/9/2017 The Association for Research in Vision and Ophthalmology Copyright © 2017. All rights reserved.

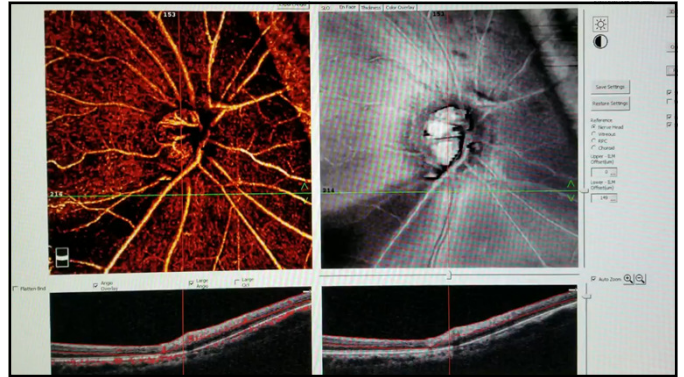
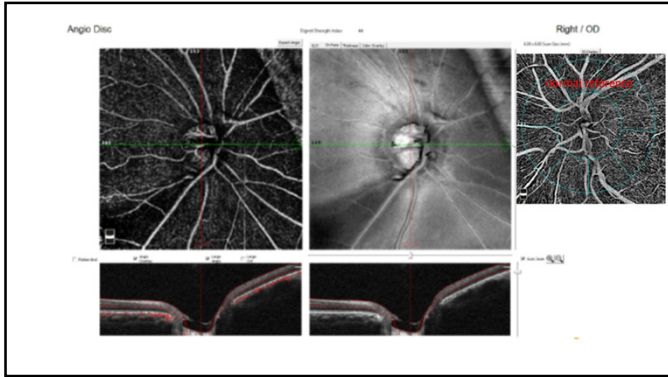


history

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

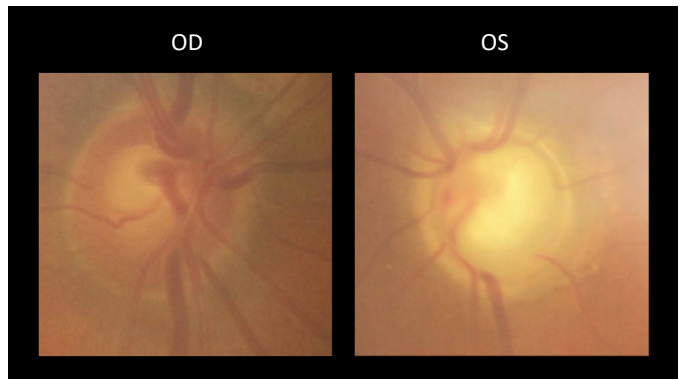


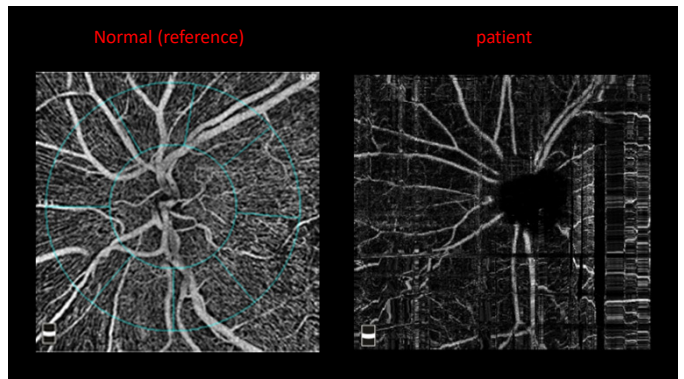
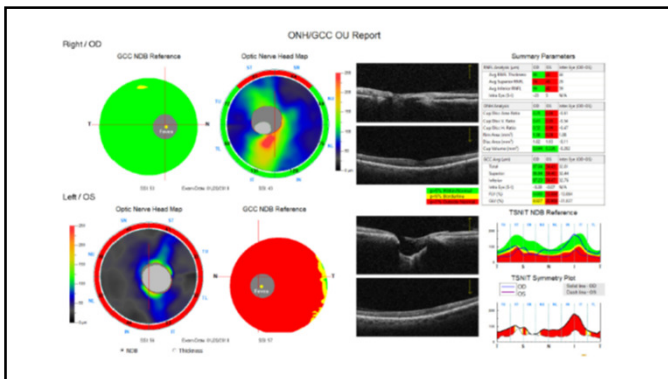
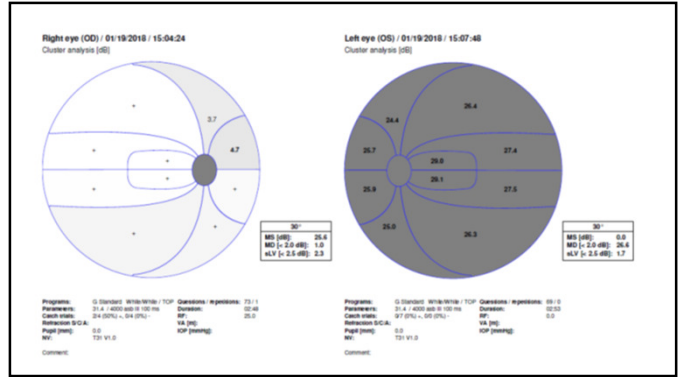
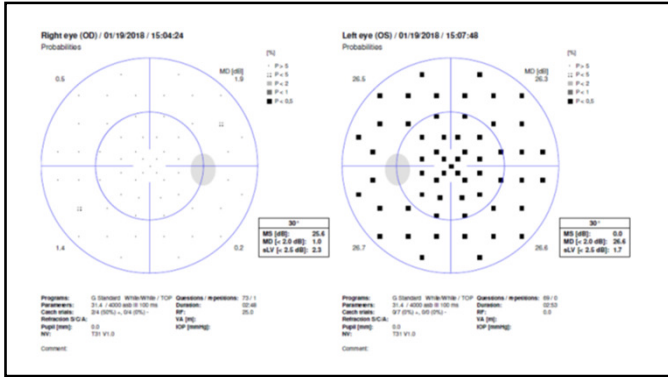




66 y/o Indian male

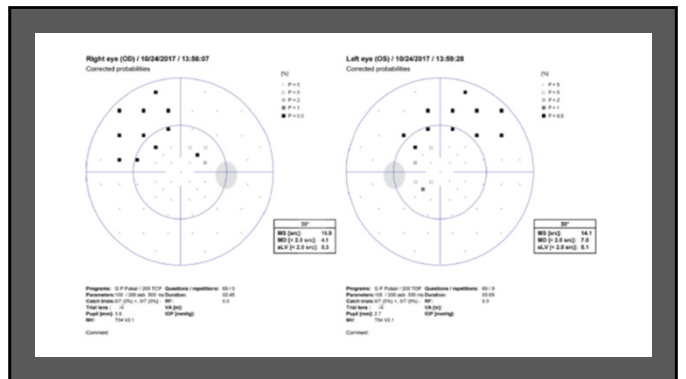
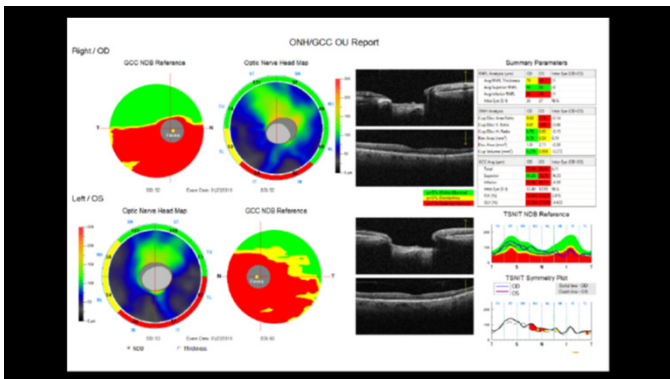
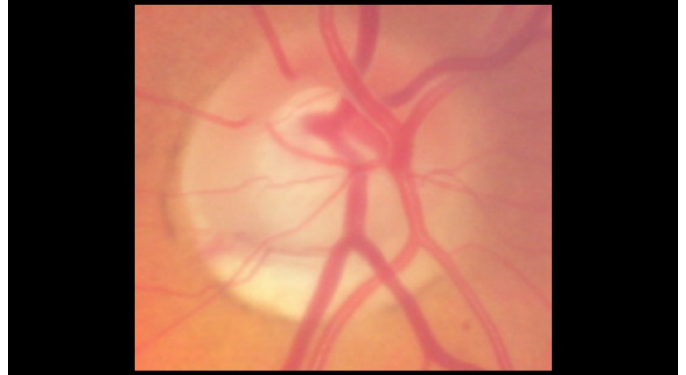
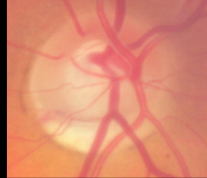
- Initial DCT IOP 25, 36
- latanoprost, dorzolamide
- SLT – 6 years ago
- treatment started OS only 2 years ago
- Intolerant to B blockers, and brimonidine

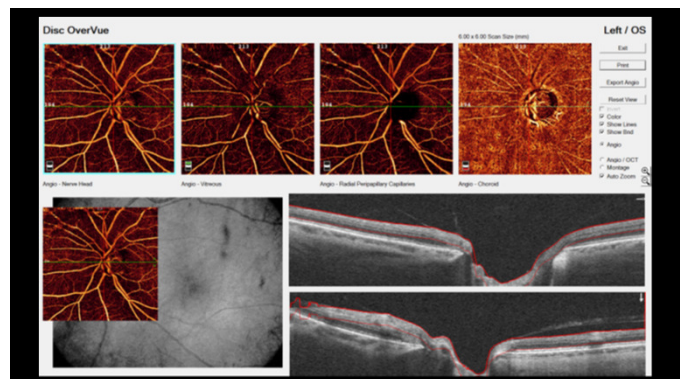
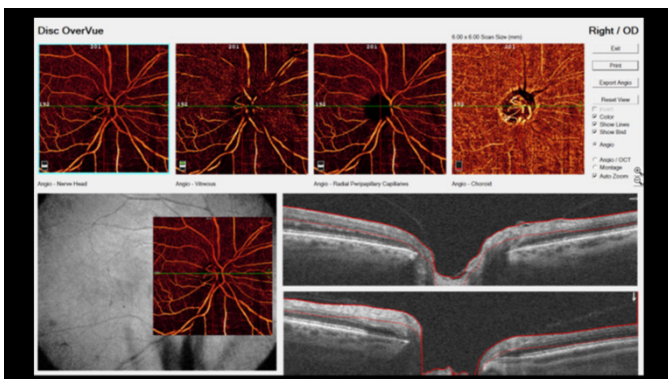
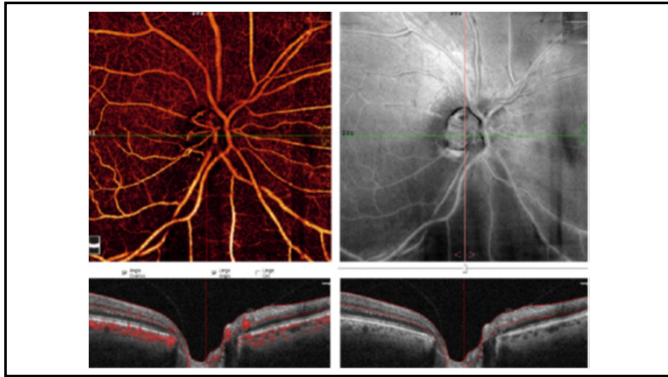


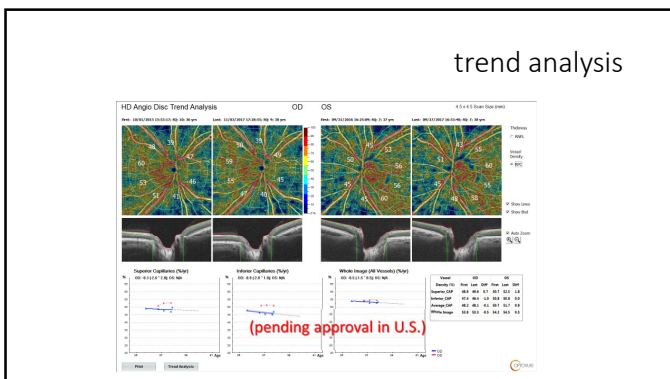
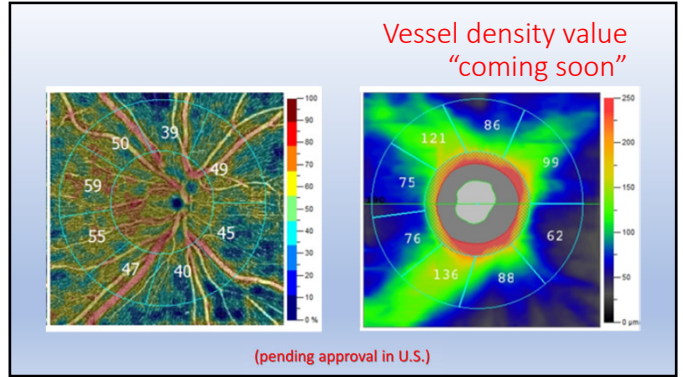


76 y/o Caucasian female

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







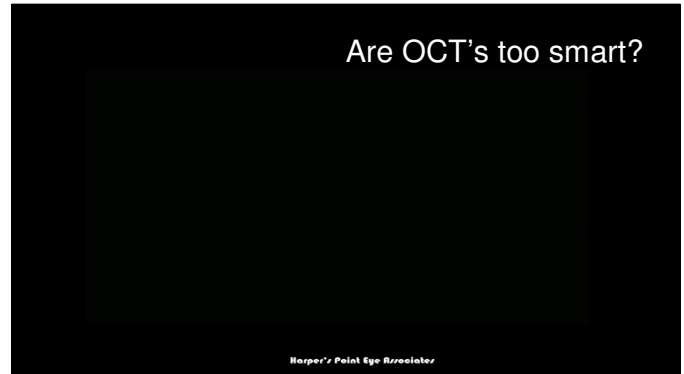
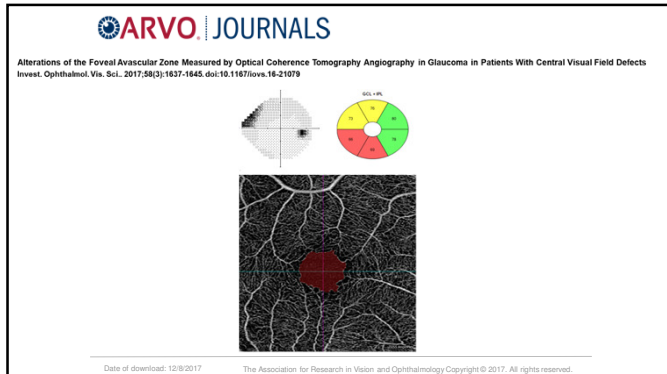
Journal Of Glaucoma

Glaucoma Diagnostic Capabilities of Foveal Avascular Zone Parameters Using Optical Coherence Tomography Angiography According to Visual Field Defect Location

Kwon, Junki MD¹; Choi, Jaewan MD, PhD¹; Shin, Joong Won MD²; Lee, Jiyun MD³; Kook, Michael S. MD, PhD⁴

Journal of Glaucoma: December 2017 - Volume 26 - Issue 12 - p 1120-1129

Conclusions: The Foveal Avascular Zone perimeter had good diagnostic capability in differentiating glaucomatous eyes with Central Visual Field Defects from normal eyes, and may be a potential diagnostic biomarker for detecting glaucomatous patients with Central Visual Field Defects.



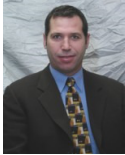

Now that we can measure it,
how can we change it?

- Decrease IOP significantly
- Measure Diastolic Perfusion Pressure
- Look for over treatment of high blood pressure
- Counsel hydration / lifestyle
- Consider topical medications which may augment blood flow

classic toys



1990's

Alon Harris, M.Sc., Ph.D.
Lecturer Professor of Ophthalmology, Professor of Physiology and Biophysics, Director, Glaucoma Research and Diagnostic Center

“I think that the only medications that have a rationale to improving blood flow when applied topically are carbonic anhydrase inhibitors”


1990's

THE EFFECTS ON IOP AND OCULAR BLOOD FLOW (OBF) OF 0.2% BRIMONIDINE

Vetruigno M, Gigante G, Cantatore F, Cardia L

Dept. of Ophthalmology - University of Bari, Italy

Conclusions: brimonidine is effective in the therapy of glaucoma in that it combines hypotensive efficacy and choroidal perfusion increase around the optic nerve head.



THE ROYAL COLLEGE OF OPHTHALMOLOGISTS

February 1999

The effect of once-daily latanoprost on intraocular pressure and pulsatile ocular blood flow in normal tension glaucoma.

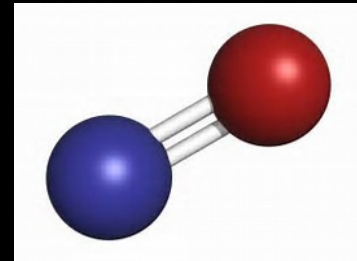
Conclusions: Once-daily treatment with 0.005% latanoprost provides a significant and stable IOP reduction in the majority of NTG patients after short-term treatment. **This is accompanied by a significant increase in POBF.**



new toys



Nitric Oxide (NO)



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



NO in non-ocular pathophysiology

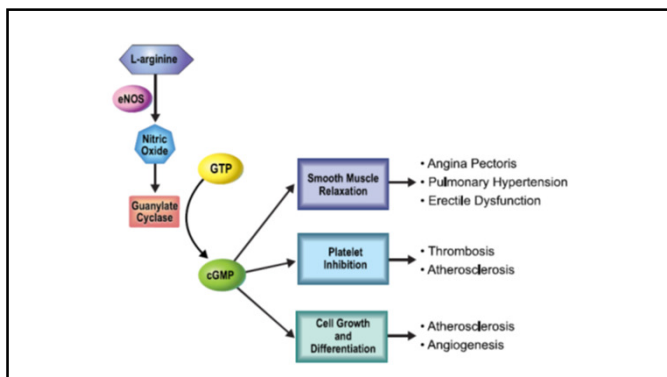
- eNOS reduces production of NO which then reduces the production of cGMP.
- cGMP dysregulation plays a role in many human disease process related to vasoconstriction and / or vasospasm

NO in non-ocular pathophysiology

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

Increasing cGMP levels treats

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

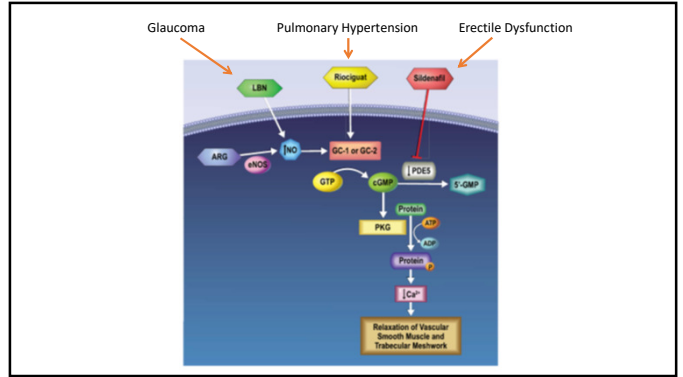


Bausch & Lomb / Nicox latanoprostene bunod VYZULTA

- 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.

new and now available

BAUSCH + LOMB

Nitric Oxide (NO) in the optic nerve

- NO donors decrease vascular resistance by relaxing smooth muscle

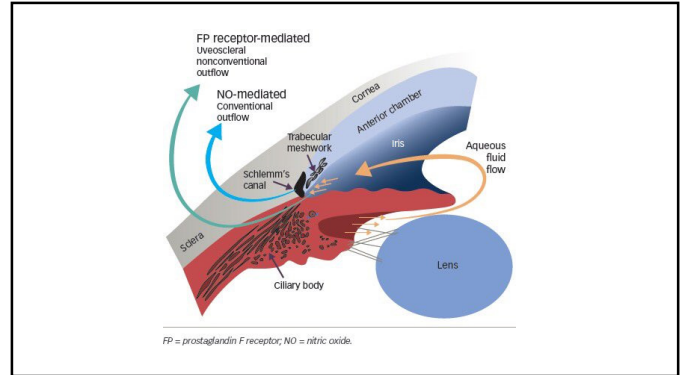
Latanoprostene Bunod 0.024% in Subjects With Open-angle Glaucoma or Ocular Hypertension: Pooled Phase 3 Study Findings

Weinreb, Robert N. MD; Liebmann, 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.

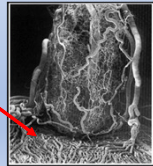
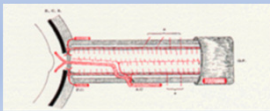
Bausch & Lomb / Nicox - latanoprostene bunod "VYZULTA"

- 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



Latanoprostene Bunod

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



Nitric Oxide Pipeline

- Bimatoprost + NO donator
- CAI + NO donator

RHOPRESSA[®]

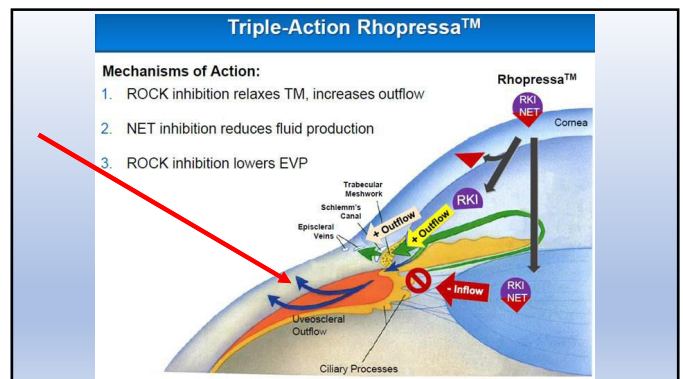
(netarsudil ophthalmic solution .02%)
Aerie Pharmaceuticals, Inc.

(approved and coming in March 2018)

Rhopressa

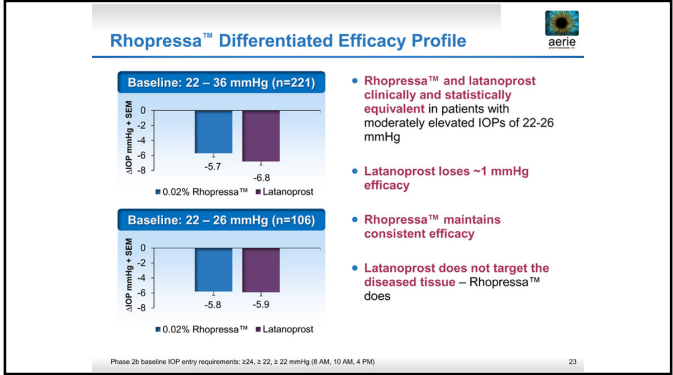
(netarsudil ophthalmic solution .02%)

- Rho kinase inhibition (“ROCK” inhibitor)
- QD dosing
- Complimentary to prostaglandins
- Reduction of episcleral venous pressure



•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



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

Pipeline

- Roclatan – rho kinase inhibitor + PGA (possible 2018)

Rhopressa™ and Rociatan™ Potential Product Advantages

Rhopressa™ Positioning

Potential drug of choice as adjunctive therapy to PGAs when additional IOP lowering is desired

Rhopressa™ Advantages

- Efficacy vs. *other adjunctive therapies*
- QD PM dose
- Lack of serious and systemic drug-related AE's

Rociatan™ Positioning

Potential drug of choice for patients requiring maximal IOP lowering

Rociatan™ Advantages

- Efficacy vs. *all other glaucoma therapies*
- QD PM dose
- Lack of serious and systemic product-related AE's

References:

1. Vyzulta™ [prescribing information]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2017.
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3. Medeiros FA, Martin KR, Peace J, et al. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.
4. Kaufman PL. Latanoprostene bunod ophthalmic solution 0.024% for IOP lowering in glaucoma and ocular hypertension. *Expert Opin Pharmacother*. 2017;18(4):433-444.
5. Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. *Br J Ophthalmol*. 2015;99:738-745.
6. Kawase K, Vittitow JL, Weinreb RN, Araie M for the Jupiter Study Group. Long-term safety and efficacy of latanoprostene bunod 0.024% in Japanese subjects with open-angle glaucoma or ocular hypertension: the JUPITER Study. *Adv Ther*. 2016;33:1612-1627.
7. Liu J, Slight JR, Vittitow JL, et al. Efficacy of latanoprostene bunod 0.024% compared with timolol 0.5% in lowering intraocular pressure over 24 hours. *Am J Ophthalmol*. 2016;169:249-257.

Thank You!