



Retina Update

Addressing the Community Questions

Gian Paolo Giuliari, MD

Diseases and Surgery of the Retina and Vitreous

Omni Eye Services

GOA Fall Conference. Athens, Georgia. October 2022



Financial Disclosure

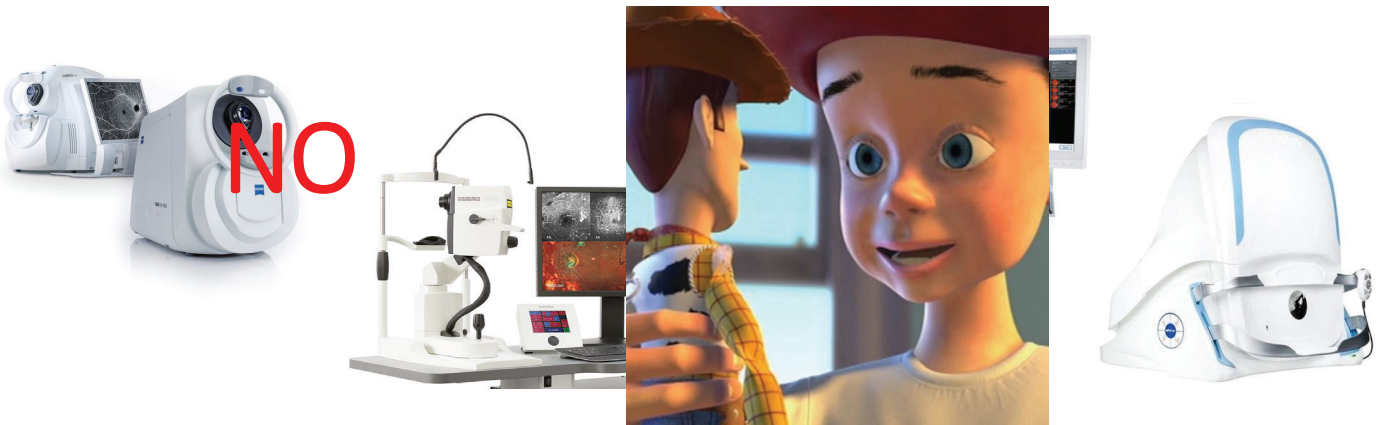
I do not have any affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of my presentation



FAQ's on my calls

- Office's "toys"
 - Do I really need an OCT and/or wide-field photography?
 - "New" role of wide-field photography in diabetic retinopathy
 - DRCR.net protocol AA
- Age related macular degeneration
 - Non exudative
 - Intravitreal injections? Is that the future?
 - Exudative
 - New anti-VEGF treatment
 - Gene therapy. Where are we?
- Retinal artery occlusion
 - Are we missing something?
- Posterior vitreous detachment

Do I really need an OCT and/or a wide field photography system?



Do I really need an OCT and/or a wide field photography system?

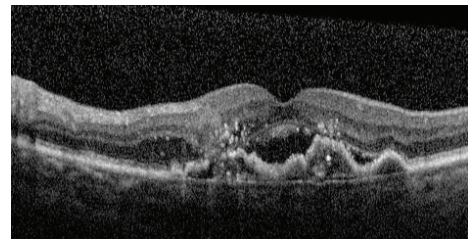
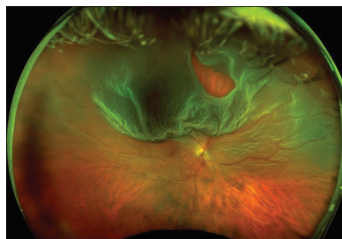


YES

Telemedicine



- *The use of electronic information and communications technologies to provide and support health care when distance separates the participants.*



Optical Coherence Tomography (OCT)



Optical Coherence Tomography (OCT)

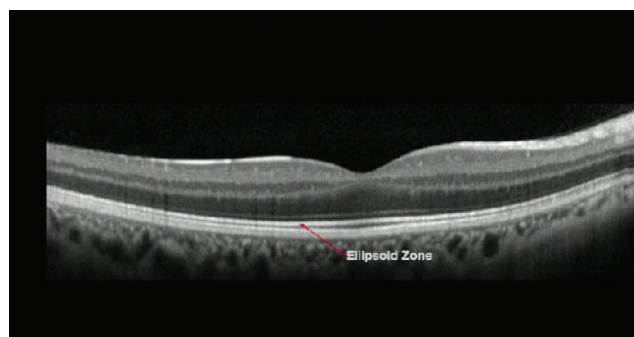
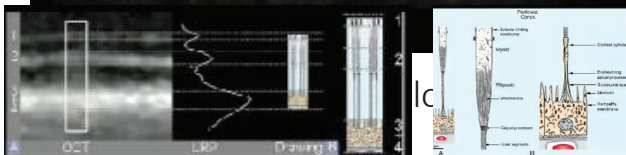
Review > Retina. 2011 Sep;31(8):1609-19. doi: 10.1097/IAE.0b013e3182247535.

Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: literature review and model

Richard F Spaide¹, Christine A Curcio

Affiliations + expand

PMID: 21844839 PMCID: PMC3619110 DOI: 10.1097/IAE.0b013e3182247535



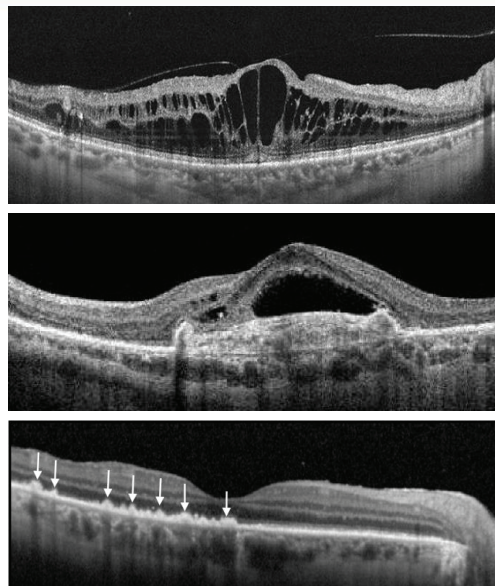
Is this the intersegment out of segment junction?

Or the reflection of all the mitochondria?

Optical Coherence Tomography (OCT)

Why OCT on every eye?

- **Macular edema/CNVM/Others**
- Pre-op/post op
- Screening for toxic meds
- Determining PVD status



Optical Coherence Tomography (OCT)

Why OCT on every eye?

- Macular edema/CNVM/Others
- **Pre-op/post op**
- Screening for toxic meds
- Determining PVD status

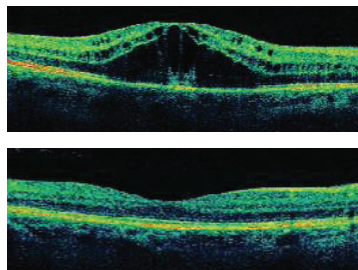
PREMIUM IOL requires PREMIUM macula



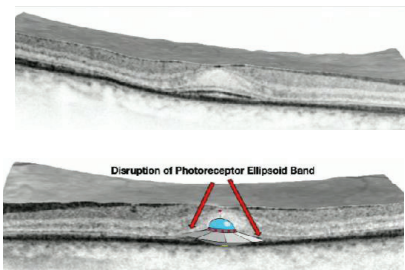
Optical Coherence Tomography (OCT)

Why OCT on every eye?

- Macular edema/CNVM/Others
- Pre-op/post op
- **Screening for toxic meds**
- Determining PVD status



Paclitaxel



Hydroxychloroquine

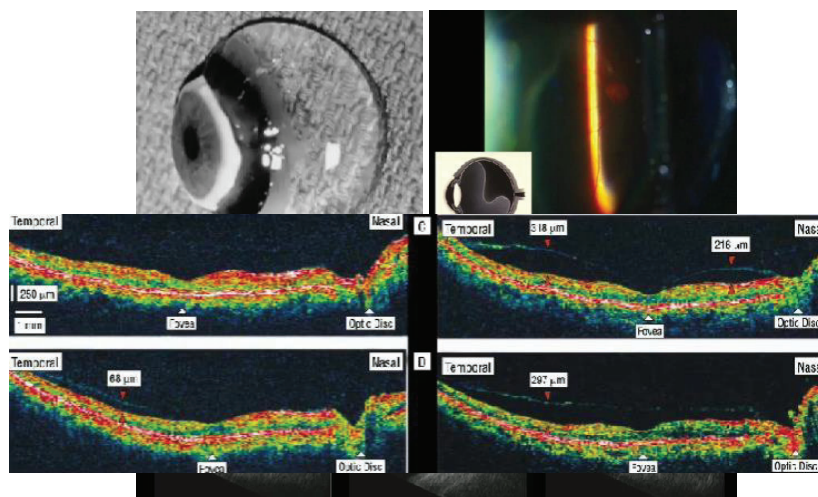
Smit S. et al. Arch Ophthalmol 2008;126:1605



Optical Coherence Tomography (OCT)

Why OCT on every eye?

- Macular edema/CNVM/Others
- Pre-op/post op
- Screening for toxic meds
- **Determining PVD status**



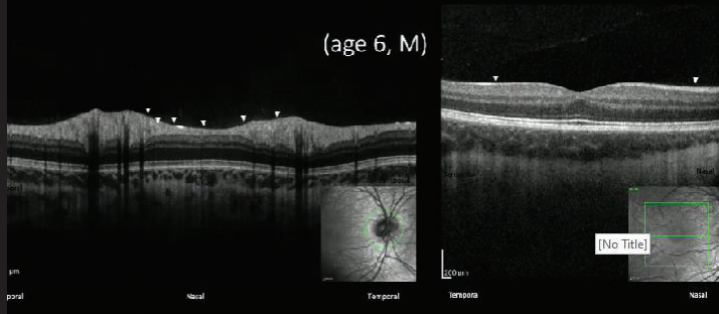
Sebag J. Imaging Vitreous. Eye 2002

Uchino E. Arch Ophthalmol. 2001 Oct;119(10):1475-9



" Stage A- NO RNFL Separation! "

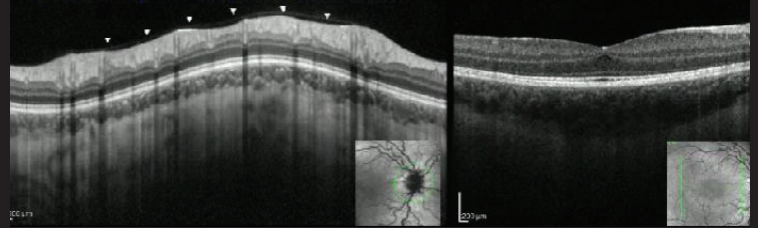
(age 6, M)



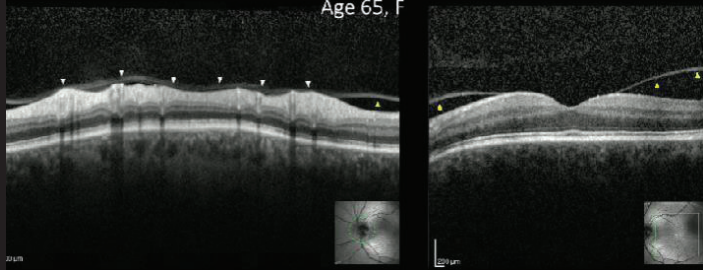
Stage B – Beginning !

"Lamellar RNFL Separation Between Nerve Vessels"
(age 12, M)

*Distinct linear signal showing the initiation of PVC separation

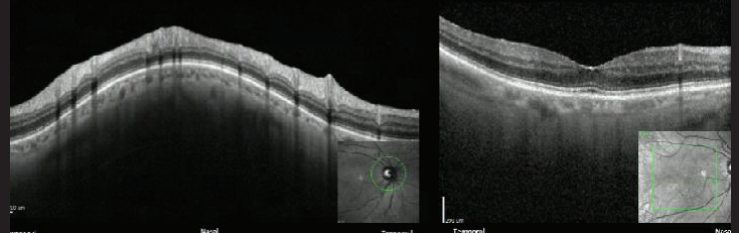


Stage C: Papillo-Macular Bundle Separation with Fovea Adhesion (Partial PVD with VMA) Age 65, F



" Stage D- DONE ! "

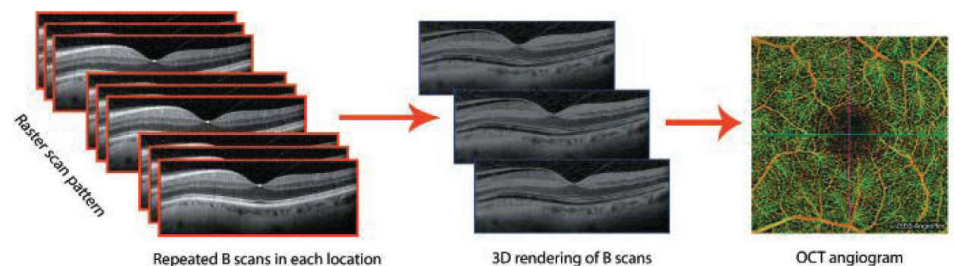
Empty Vitreous over RNFL
(Age 82, F)



Optical Coherence Tomography (OCT)

BONUS

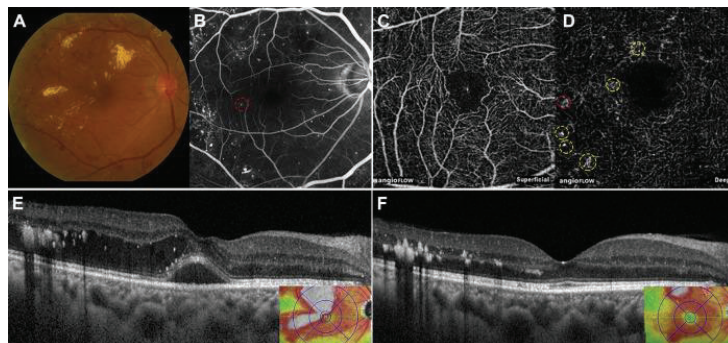
Should we upgrade to OCT angiography?



Optical Coherence Tomography (OCT): OCT angiography

- Is it better than FA and an OCT?

- Fast
- Noninvasive

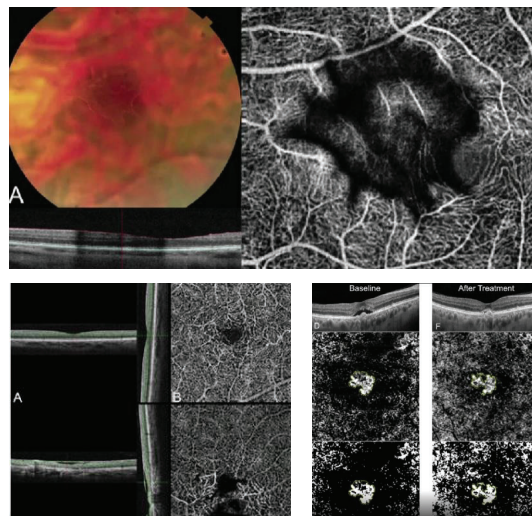


New insights to clinical diseases?

Optical Coherence Tomography (OCT): OCT angiography

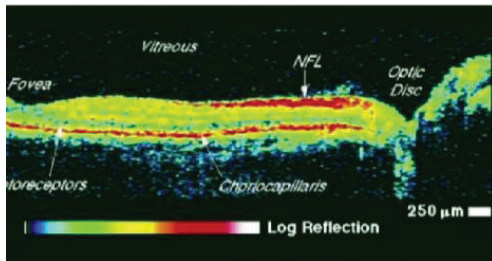
Cons

- Image acquisition artifacts
- False positives and negatives common
- Tight correlation with OCT is needed
- No information on vascular permeability
- Expensive and reimbursement issues

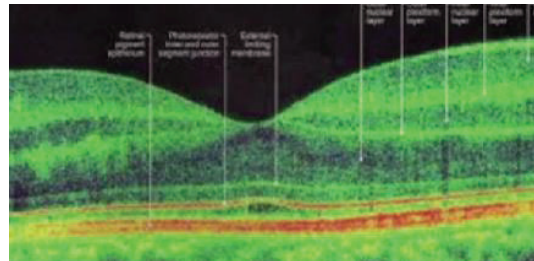


Optical Coherence Tomography (OCT): OCT angiography

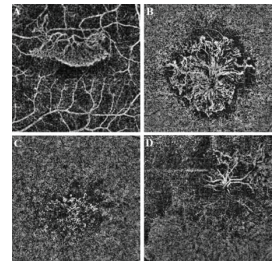
Should we upgrade?



2000



2022



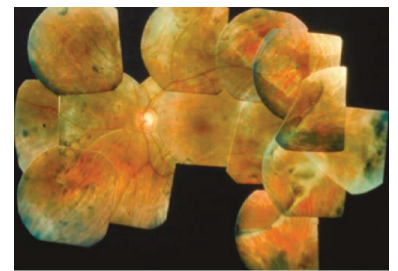
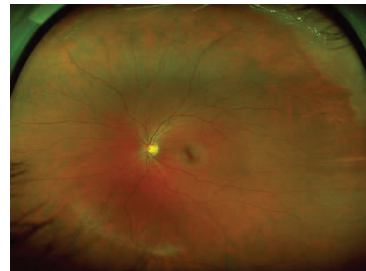
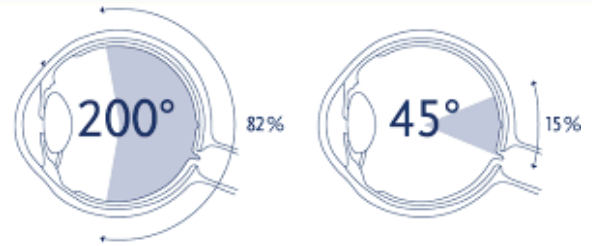
OCTa is advanced technology ... in search of a problem

Wide-field photography



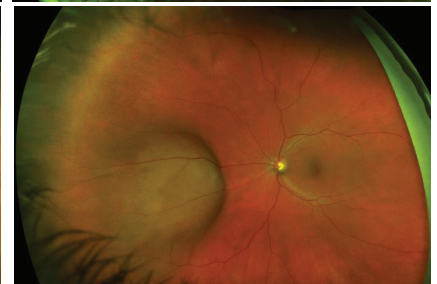
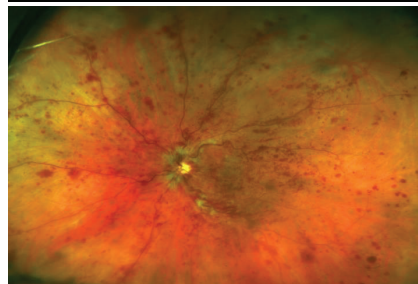
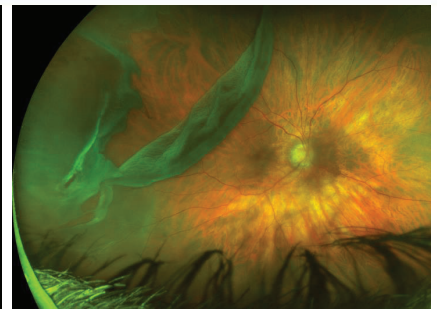
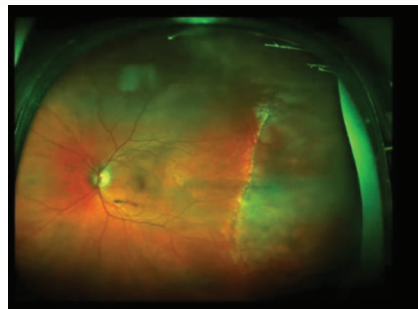
Wide-field photography

- Advantages
 - Wider field of view
 - What about montages?
 - FA areas of non perfusion
 - Patient education



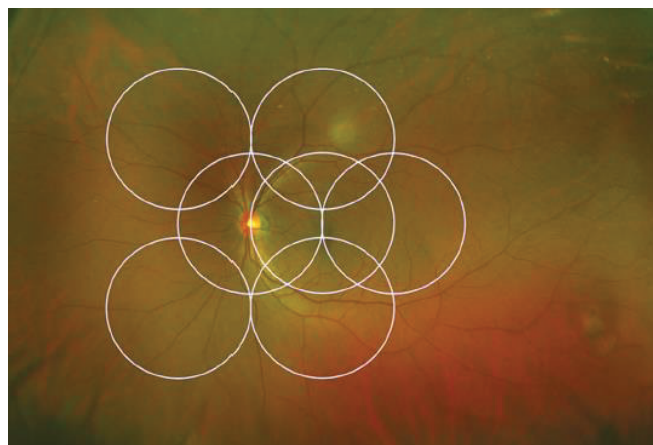
Wide-field photography

- **Color photo**
 - Diabetic retinopathy: PPL
- Autofluorescence (AF)
- Fluorescein angiography (FA)
- Indocyanine angiography (ICG)



Wide-field photography: Diabetic retinopathy and PPL

- **Color photo**
 - **Diabetic retinopathy: PPL**
- Autofluorescence (AF)
- Fluorescein angiography (FA)
- Indocyanine angiography (ICG)

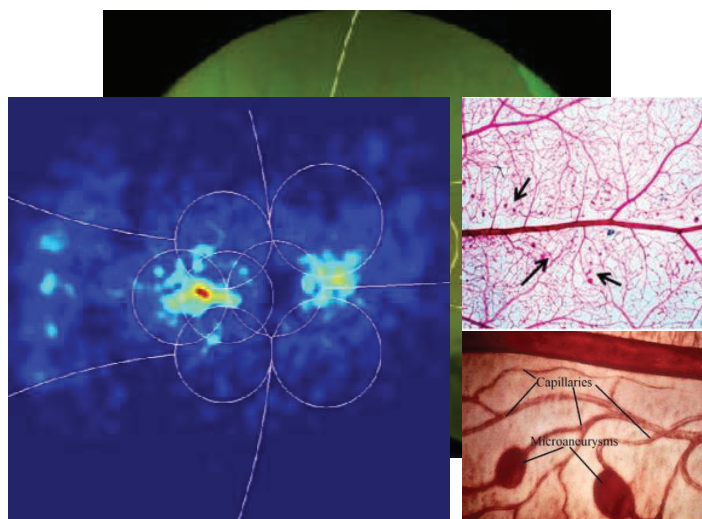


Does the additional retinal area visualized by UWF benefit clinical care?

Wide-field photography: Diabetic retinopathy and PPL

Predominantly Peripheral Lesions (PPL)

- When more DR lesions are located outside the ETDRS field
- DRCR.net Protocol AA
- PPL present in 41% of eyes
- PPL lesions
 - 80-95% H/MA
- H/MA counts might provide improved prediction of DR progression



Wide-field photography: Diabetic retinopathy and PPL

Baseline PPL and DR progression at 4 years in eyes with no or mild NPDR at baseline
(by ETDRS photos at baseline and follow up, N=109)

DR Change	Eyes <u>WITHOUT</u> Predominantly Peripheral Lesions at baseline (N=54)	Eyes <u>WITH</u> Predominantly Peripheral Lesions at baseline (N=55)	P value*	P value†
2 steps or more	11% (6)	35% (19) 3.2x↑ risk	0.0036	0.0316
PDR Onset	6% (3)	25% (14) 4.2x↑ risk	0.0069	0.0816

Silva, et al. Ophthalmology 2015



Wide-field photography: Diabetic retinopathy and PPL

Predominantly Peripheral Lesions (PPL)

- HMA-PPL associated increase of:
- 30% for anemia
- 38% for microalbuminuria
- 22% for overt nephropathy
- 12% chronic kidney disease

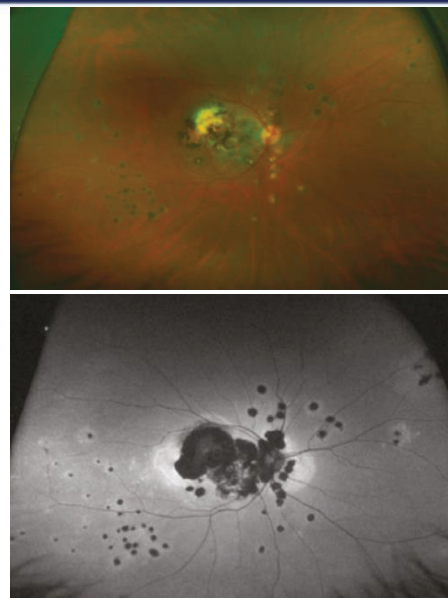
- Higher risk of DR progression
- Particularly pertinent in telemedicine where the peripheral retina changes are not routinely evaluated

Silva, et al. ARVO 2019



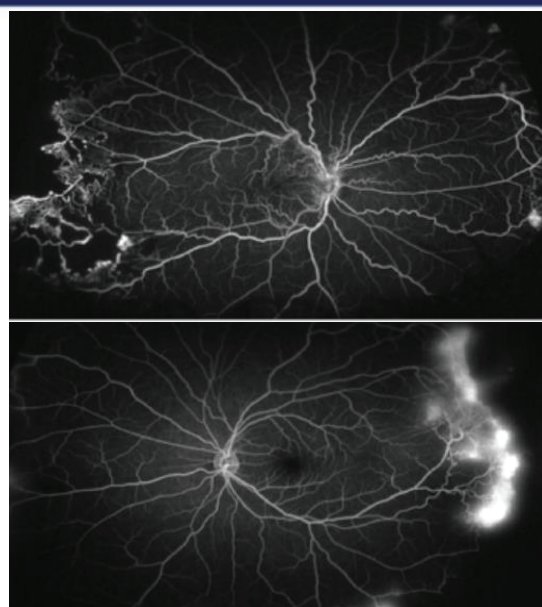
Wide-field photography

- Color photo
 - Diabetic retinopathy: PPL
- **Autofluorescence (AF)**
- Fluorescein angiography (FA)
- Indocyanine angiography (ICG)



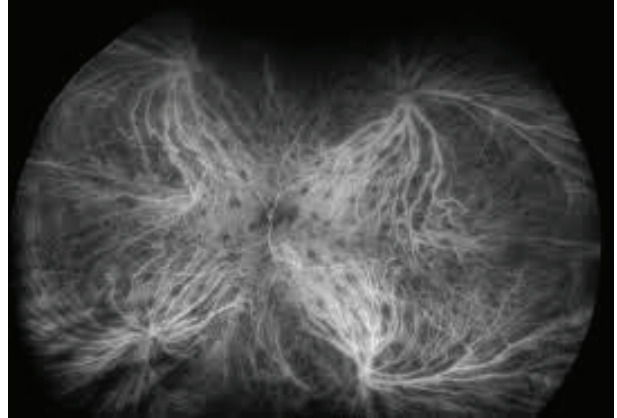
Wide-field photography

- Color photo
 - Diabetic retinopathy: PPL
- Autofluorescence (AF)
- **Fluorescein angiography (FA)**
- Indocyanine angiography (ICG)



Wide-field photography

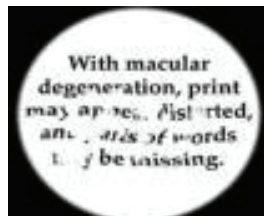
- Color photo
 - Diabetic retinopathy: PPL
- Autofluorescence (AF)
- Fluorescein angiography (FA)
- **Indocyanine angiography (ICG)**



Age related macular degeneration

Prevalence

- Leading cause of severe vision loss in the Western World
 - Decreased VA and contrast sensitivity
 - Metamorphopsia and scotomas



- Epidemiol Rev. 1995;17:347-360
- Arch Ophthalmol. 2004; 122:564-572

Age related macular degeneration

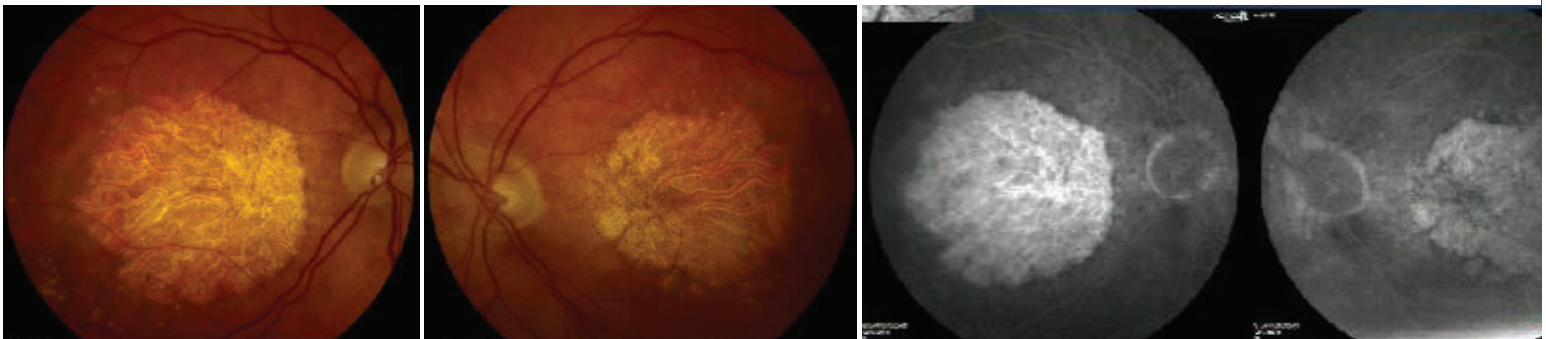
- Two forms of AMD
 - Non-neovascular (Dry) AMD
 - Drusen → geographic atrophy
 - Neovascular (Wet) AMD
- 90% of vision loss results from Wet AMD



• Arch Ophthalmol 2004;122:564-572

Aged related macular degeneration: Non exudative

- 80 year-old female with CF OU

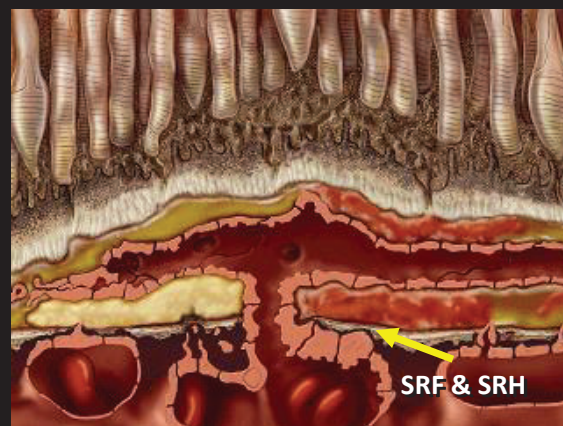
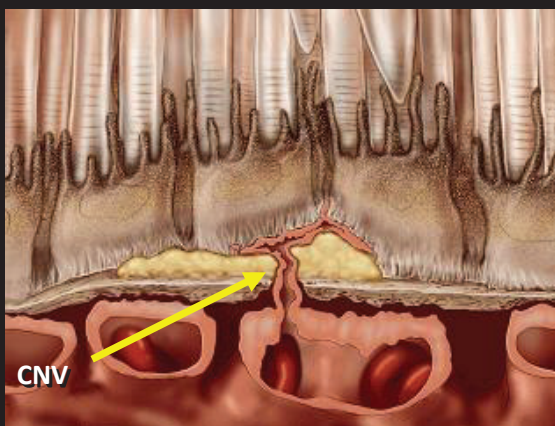
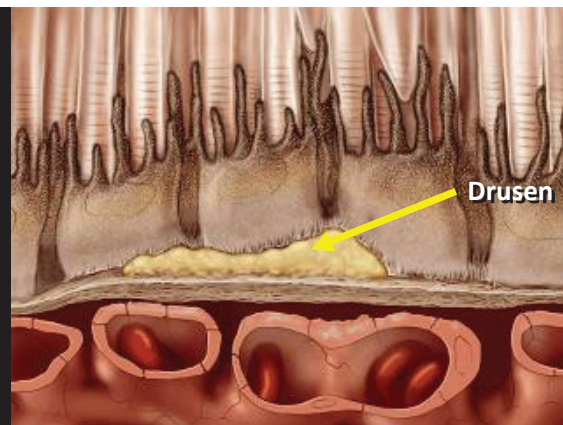
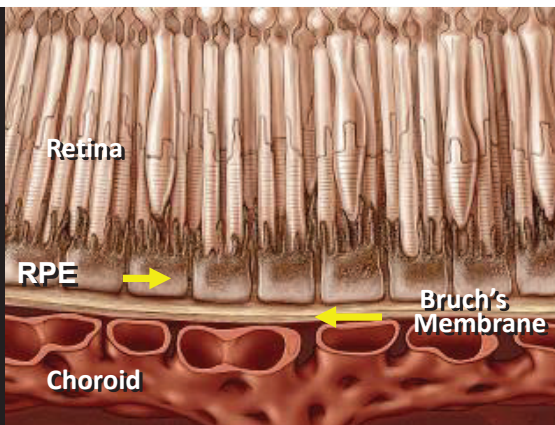
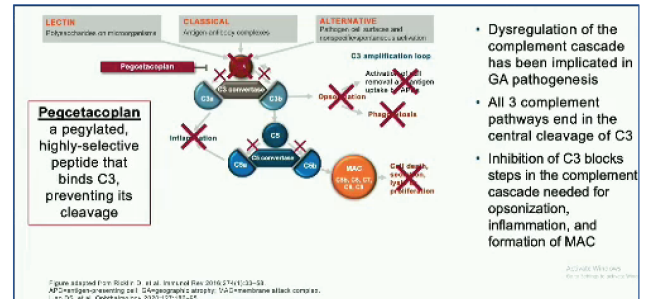
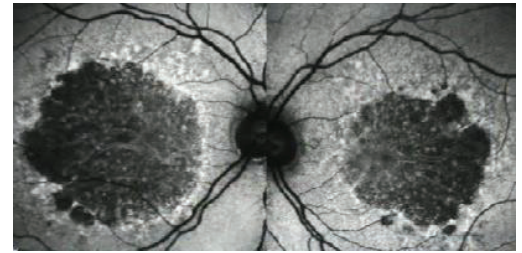
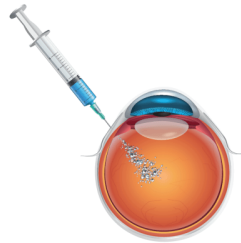


Aged related macular degeneration: Non exudative

Geographic atrophy

Management

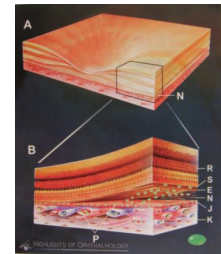
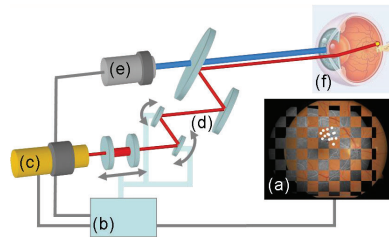
- Lifestyle
- Stop AREDS?
- Discuss possibility of pegcetacoplan
- Consider clinical trials



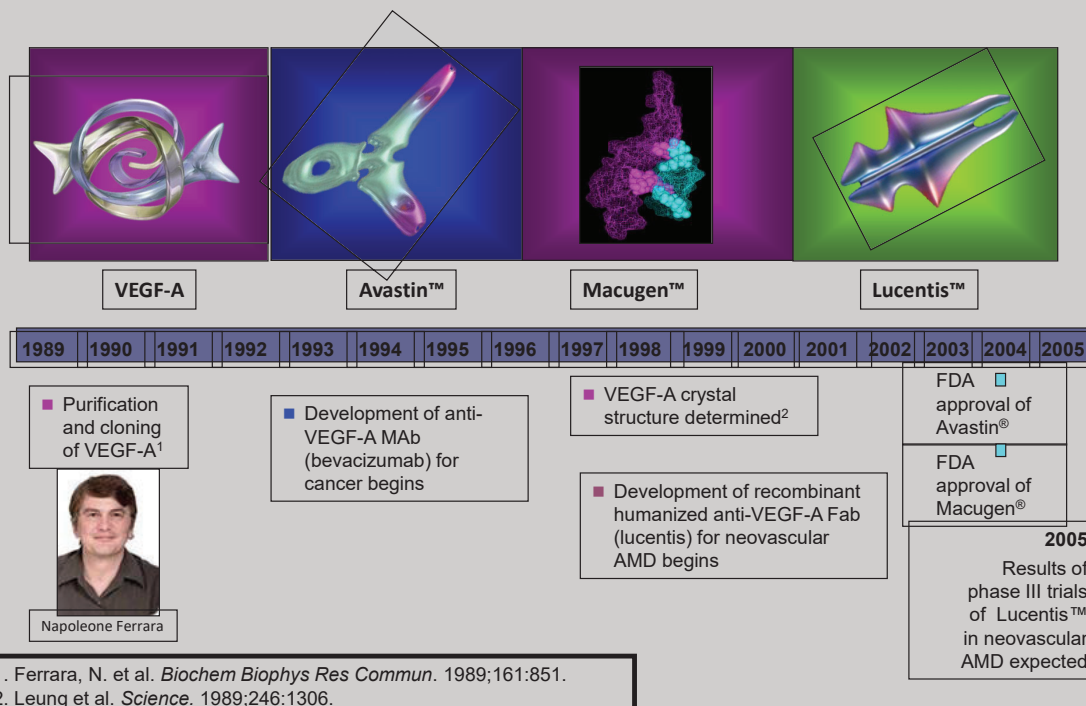
Aged related macular degeneration: Exudative

Treatments for Exudative AMD

- Thermal laser coagulation
 - MPS: Macular Photocoagulation Study
- PDT with verteporfin (Visudyne)
 - TAP: Treatment of Age-Related Macular Degeneration with Photodynamic Therapy
 - VIP: Verteporfin in Photodynamic Therapy



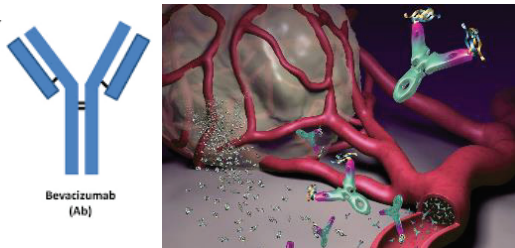
Evolution of Anti-VEGF-A Therapy



Aged related macular degeneration: Exudative

Bevacizumab (Avastin)

- First approved anti angiogenic (Colon cancer)
- Antibody against all isoforms of VEGF-A.



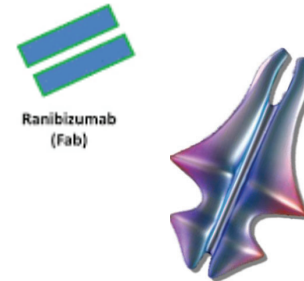
Pegaptanib (Macugen)

- Binds selectively to VEGF isoform 165
- Spares normal vasculature



Ranibizumab (Lucentis)

- Humanized fragment of a monoclonal Ab
- VEGF-A pan blockade



Nat Rev Drug Discov 2004;3:391-400

Retina 2002;22:143-152

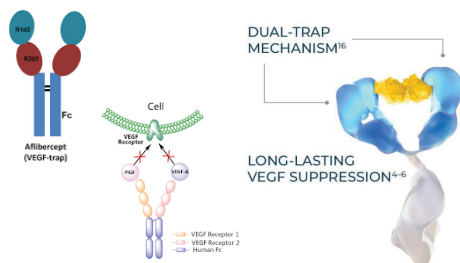
J Exp Med. 2003;198:483-489



Aged related macular degeneration: Exudative

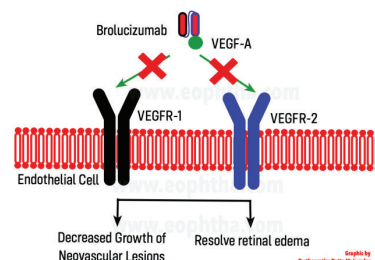
Aflibercept (Eylea)

- 115 kDa fusion protein
- IgG backbone fused to extracellular VEGF receptor sequences
 - VEGFR1 and VEGFR2



Brolucizumab (Beovu)

- 26 kDa fusion protein
- Single-chain fragment



Ophthalmology 2020;127:1345-1359

Curr Oncol Rep 2014;16:368

Ophthalmologica 2021;244:93-101

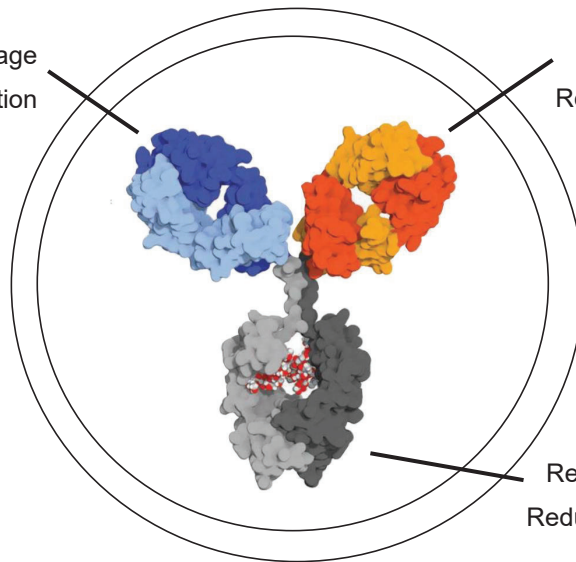
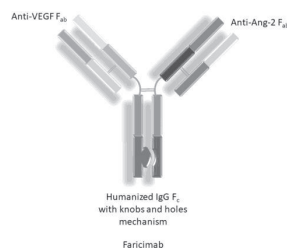


Aged related macular degeneration: Exudative

Faricimab (Vabysmo)

• First intraocular Bispecific Ab

- Anti-VEGF Fab
- Anti-Ang 2 Fab



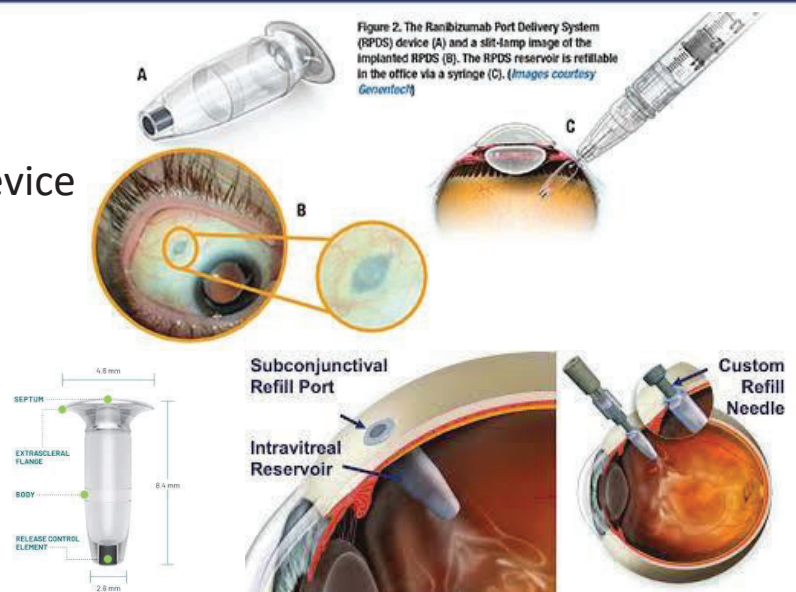
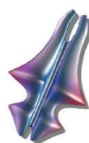
Eye 2020;34:802-804



Aged related macular degeneration: Exudative

Port delivery system (Susvimo)

- Scleral base intraocular reservoir device
- Refill in the office
- Ranibizumab 10x concentrated
- Solid silicon except the septum

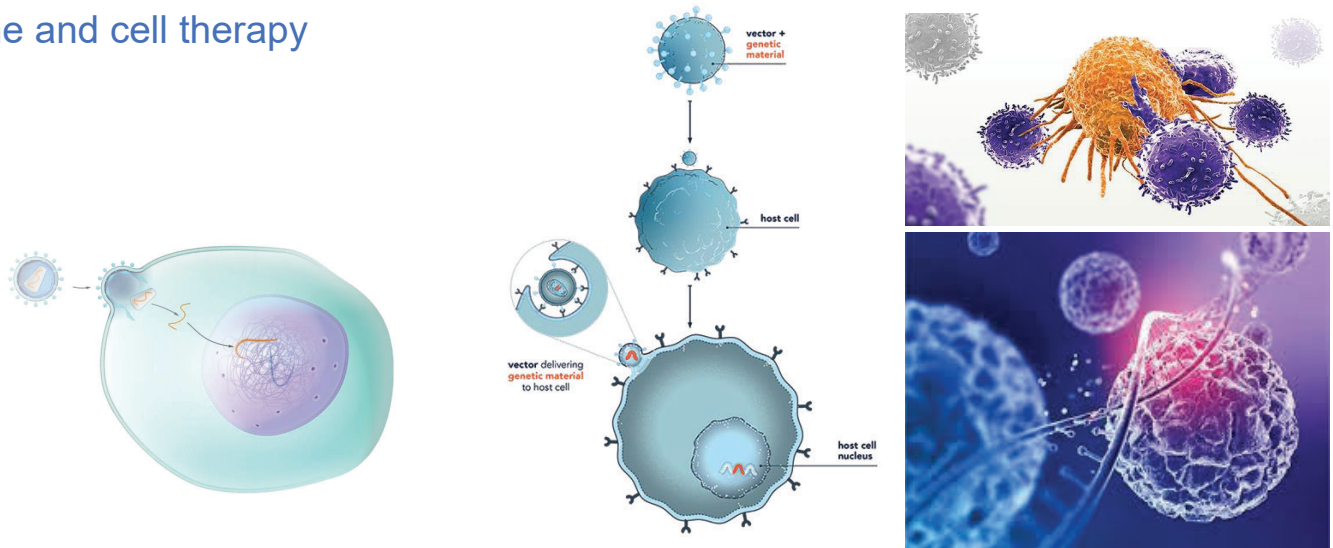


Ophthalmology 2022;129:296-307



Aged related macular degeneration: Gene and cell therapy

Gene and cell therapy



Aged related macular degeneration: Gene and cell therapy

Subretinal and suprachoroidal delivery

RGX314
Phase I/IIa Study

PPV retinotomy

Vector AAV8
Anti-VEGF fAb

ORBIT subretinal delivery system

Subretinal via suprachoroidal

Vector AAV2
Transgene C factor 1

FOCUS. GT005
Phase I/II Study
Geographic atrophy

Uveitis

- Triamcinolone acetate (Xipere)

RGX314
AAVIATE Phase II

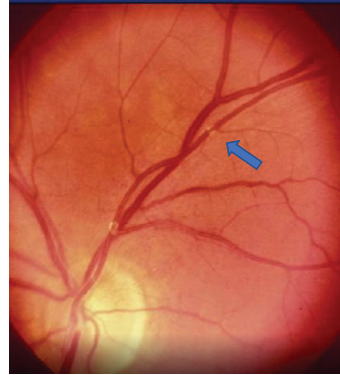
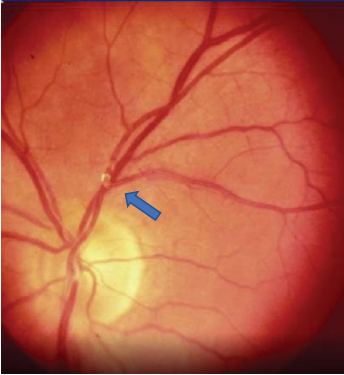
Suprachoroidal injection

Suprachoroidal Illuminated Microcatheter Delivery

OFFICE PROCEDURE!!

Retinal artery occlusion: What do I do now?

- Nov 1959, 52-year-old male transient visual symptoms OD
 - Tx with heparin and coumadin
 - OU 20/20



Photos James A. Garrity MD



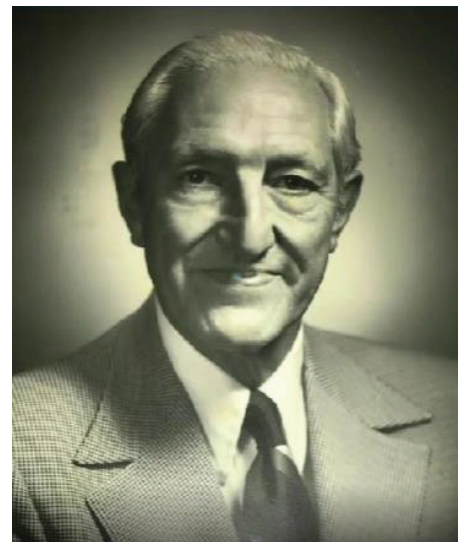
Retinal artery occlusion

> JAMA. 1961 Oct 7;178:23-9. doi: 10.1001/jama.1961.03040400025005.

Significance of bright plaques in the retinal arterioles

R W HOLLENHORST

PMID: 13908419 DOI: 10.1001/jama.1961.03040400025005



Retinal artery occlusion

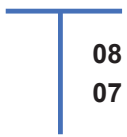
- 47 year-old Caucasian Male

- Visual acuity



20/20
20/20

- Confrontational visual field
 - Concentric decrease OD

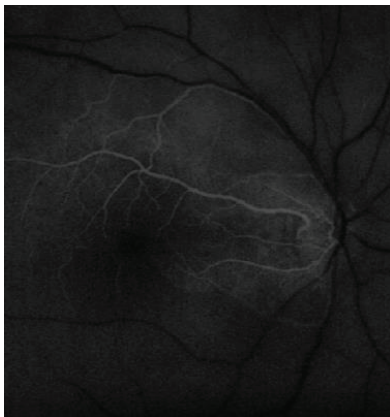


08 mmHg
07 mmHg

- Pupils isocoric and normoreactive
- Muscle balance normal



Retinal artery occlusion



19 seconds



25 seconds



47 seconds

Retinal artery occlusion

- Ophthalmologists are required to make the diagnosis
 - Amaurosis fugax, transient obscurations

Systemic work up

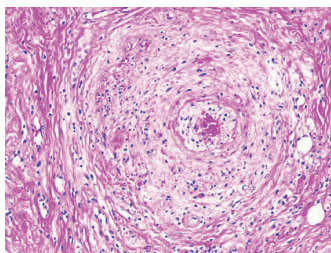
- ESR/CRP
- BP & EKG
- Cardiac Echo
- Carotid Ultrasound
- CBC
- Anti-Phospholipid Ab
- Diffuse weighted MRI
- LES
- Anti-thrombin III
- Homocystinuria
- Prot C or S
- Factor V Leiden
- Susac Syndrome

Retinal artery occlusion

- Ophthalmologists are required to make the diagnosis
 - Amaurosis fugax, transient obscurations

Systemic work up

- **ESR/CRP**
- BP & EKG
- Cardiac Echo
- Carotid Ultrasound
- CBC
- Anti-Phospholipid Ab



- Diffuse weighted MRI
- LES
- Anti-thrombin III
- Homocystinuria
- Prot C or S
- Factor V Leiden
- Susac Syndrome

Retinal artery occlusion

> Exp Eye Res. 2004 Mar;78(3):723-36. doi: 10.1016/j.exer.2003.03.002.14-8.

Central retinal artery occlusion. Retinal survival time

Sohan Singh Hayreh¹, M Bridget Zimmerman, Alan Kimura, Ashish Sanon

Affiliations + expand

PMID: 15106952 DOI: 10.1016/j.exer.2003.03.002.14-8

97-240 min

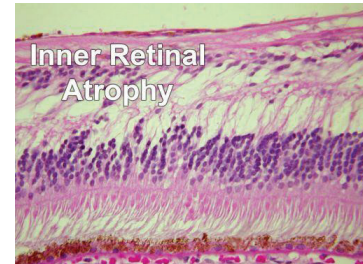
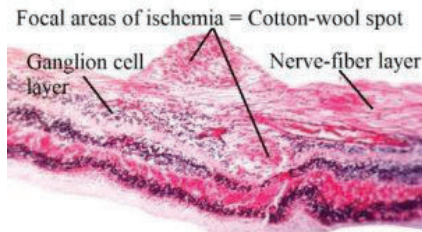
Abstract

Purpose: To investigate the retinal survival time following central retinal artery occlusion (CRAO).

Methods: In 38 elderly, atherosclerotic and hypertensive rhesus monkeys, transient CRAO (varying from 97 to 240 min) was produced by temporarily clamping the CRA at its site of entry into the optic nerve. Stereoscopic color fundus photography, fluorescein fundus angiography, electroretinography (ERG), and visual evoked potential (VEP) recording were performed before and during CRA clamping, after unclamping, and serially thereafter. After unclamping of the CRA, the animals were followed for variable lengths of time (median duration 8.14 weeks). Finally, the eyes and optic nerves were examined histologically. The data on ERG changes were analyzed in the following four time frames: (1) baseline before CRA clamping, (2) during CRA clamping, (3) immediately after unclamping, and (4) at the end of follow-up. Duration of CRAO was divided into four groups: 97, 105-120, 150-165, and > or = 180 min.

Results: A 'negative ERG' appeared during CRA clamping. With removal of the CRA clamp, there was b-wave recovery, with differential rates of recovery of ERG-eyes with shorter CRAO recovered sooner than those with longer occlusion. On removal of clamp, recovery was seen in scotopic 24 dB b-wave, photopic 0 dB single flash b-wave and 30 Hz flicker, with the b/a ratio of the combined rod and cone response and selective rod response showing statistically significant differences amongst the shorter and longer periods of CRAO. A delayed normalization of the depressed b/a ratio immediately after CRA reperfusion may indicate high-grade ischemic damage. At the final follow-up test session, no clear-cut derangement of any ERG parameter was seen for any group, with subtotal b-wave amplitude recovery for all groups. Longer CRAO produced incomplete VEP recovery. On histology, in the macular retina, eyes with CRAO for 97 min showed practically no damage, but duration of CRAO was found to be significantly associated with the amount of damage in the ganglion cell layer ($p = 0.009$) and inner nuclear layer ($p = 0.017$). Outer nuclear and plexiform layers and photoreceptors showed no damage at all with CRAO. There was no significant association of the ERG measures and histologic changes with any of the residual retinal circulation variables.

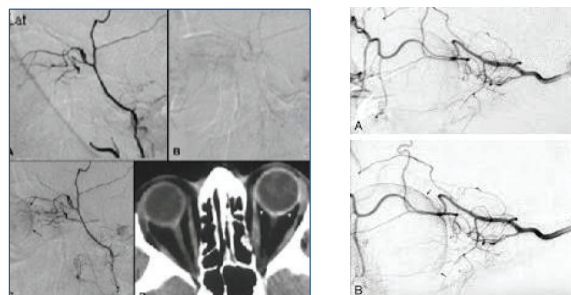
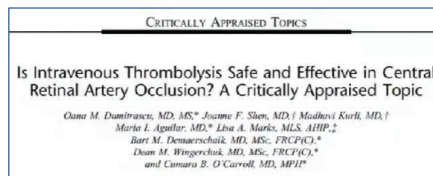
Conclusions: Our electrophysiologic, histopathologic and morphometric studies showed that the retina of old, atherosclerotic, hypertensive rhesus monkeys suffers no detectable damage with CRAO of 97 min but above that level, the longer the CRAO, the more extensive the irreversible damage. The study suggests that CRAO lasting for about 240 min results in massive irreversible retinal damage.



Retinal artery occlusion

Conservative treatment

- Digital Massage
- AC tap
- Carbogen
- Nitroglycerin
- YAG embolysis
- Others



Randomized Controlled Trial > Ophthalmology. 2010 Jul;117(7):1367-75.e1.
doi: 10.1016/j.ophtha.2010.03.061.

Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial

Martin Schumacher¹, Dieter Schmidt, Bernhard Jurkies, Christine Gall, Isabel Wierke, Claudia Schmoor, Herbert Maier-Lenz, Laszlo Solymosi, Hartmut Brueckmann, Aljoscha S Neubauer, Armin Wolf, Nicolas Felgen, EAGLE Study Group

Collaborators, Affiliations + expand

PMID: 20609991 DOI: 10.1016/j.ophtha.2010.03.061

Eagle Study

Abstract

Purpose: The reported outcomes of central retinal artery occlusion (CRAO) with or without treatment vary considerably. Although local intra-arterial fibrinolysis (LIF) using recombinant tissue plasminogen activator (rtPA) is a promising treatment, outcomes have not been compared in randomized trials.

Design: Prospective randomized multicenter clinical trial (the European Assessment Group for Lysis in the Eye Study) to compare treatment outcome after conservative standard treatment (CST) and LIF for acute nonarteritic CRAO.

Participants: Between 2002 and 2007, 9 centers in Austria and Germany recruited 84 patients (40 received CST, 44 received LIF), and data for 82 patients were analyzed.

Methods: Patients (age 18-75 years) with CRAO, symptoms for 20 hours or less, and best-corrected visual acuity (BCVA) <0.5 logarithm of the minimum angle of resolution (logMAR) were randomized to the CST or LIF group.

Main outcome measures: The primary end point was BCVA after 1 month; the secondary end point was safety.

Results: The mean interval between first symptoms and therapy was 10.99 ± 5.49 hours (CST) and 12.78 ± 5.77 hours (LIF). The mean BCVA (logMAR) improved significantly in both groups (CST: -0.44 [standard deviation 0.55]; LIF: -0.45 [standard deviation 0.55]; both $P < 0.0001$) and did not differ between groups ($P = 0.69$). Clinically significant visual improvement (≥ 0.3 logMAR) was noted in 60.0% (CST) and 57.1% (LIF) of patients. Two patients in the CST group (4.3%) and 13 patients in the LIF group (37.1%) had adverse reactions. Because of apparently similar efficacy and the higher rate of adverse reactions in the LIF group, the study was stopped after the first interim analysis at the recommendation of the data and safety monitoring committee.

Conclusions: In light of these 2 therapies' similar outcomes and the higher rate of adverse reactions associated with LIF, we cannot recommend LIF for the management of acute CRAO.

Financial disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Copyright 2010 American Academy of Ophthalmology. Published by Elsevier Inc. All rights reserved.

Meta-Analysis. The Neurologist;22;153-56;2017

Shumacher et al. Ophthalmology. 2010 Jul;117(7):1367-75.e1.



Retinal artery occlusion

2013



- Ischemic Stroke
 - An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.

Retinal artery occlusion

EDITORIAL

Acute Retinal Arterial Ischemia: An Emergency Often Ignored

VALÉRIE BIOUSSE

Am J Ophthalmol. 2014 Jun;157(6):119-21

Co-occurrence of Acute Retinal Artery Occlusion and Acute Ischemic Stroke: Diffusion-Weighted Magnetic Resonance Imaging Study

JUNWON LEE*, SEUNG WOO KIM*, SUNG CHUL LEE, OH WOONG KWON, YOUNG DAE KIM, AND SUK HO RYUON

Am J Ophthalmol. 2014 Jun;157(6):1231-8

Acute Silent Brain Infarction in Monocular Visual Loss of Ischemic Origin



Florian Lauda* Hermann Neugebauer* Lars Reiber* Eric Jüttler^{a, b}

^aDepartment of Neurology, University of Ulm, Ulm, ^bDepartment of Neurology, Ostalb-Klinikum, Aalen, Germany

Cerebrovasc Dis. 2015;40(3-4):151-6

- 213 patient
 - 24% with acute CNS infarction
 - 90% were asymptomatic
- 33 patients
 - 24% with acute CNS infarction
 - 38% were asymptomatic

Retinal artery occlusion

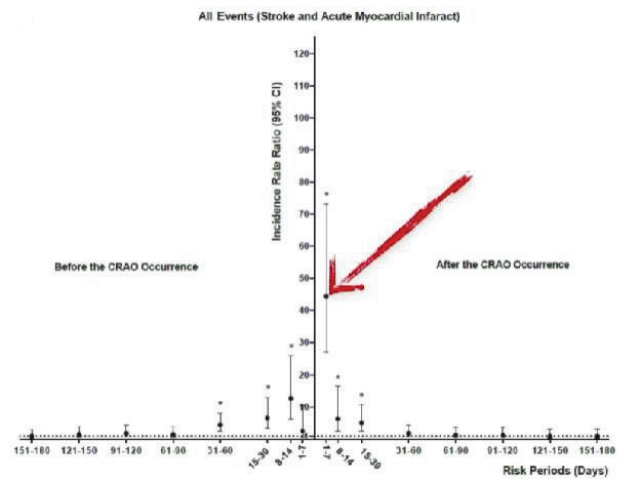



Risk and Risk Periods for Stroke and Acute Myocardial Infarction in Patients with Central Retinal Artery Occlusion

Sang Jun Park, MD, MSc,^{1,*} Nam-Kyong Choi, PhD,^{2,3,*} Bo Ram Yang, PhD,² Kyu Hyung Park, MD, PhD,² Joongsub Lee, MD, PhD,² Sun-Young Jung, PhD,² Se Joon Woo, MD, PhD²

Ophthalmology. 2015;122(11):2336-2343

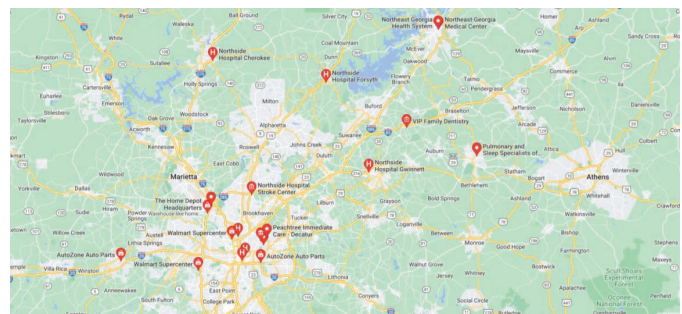
- 1655 patients
 - 10% with acute stroke/MI
 - Peak risk 7 days high risk



Retinal artery occlusion

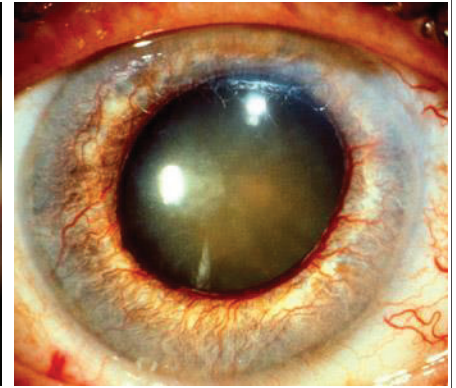
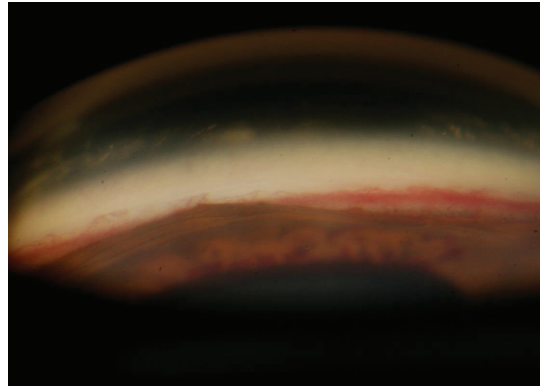
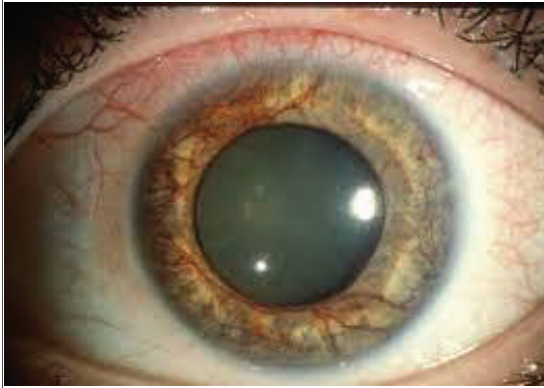
We need to follow the stroke guidelines

RAO	Time	Plan	Testing
Acute	<24 hr	Go to ED Stroke Team	Carotids prior to discharge Holter/Echo/MRI scheduled <2 wk
Subacute	24 hr - 14 days	TIA Clinic Friday night: ED if <48 hr ASA	Carotids < 24-48 hours Holter/Echo/MRI <2 wk
Chronic	>14 days	TIA Clinic ASA	Carotids within a week Holter/Echo/MRI <2 wk



Retinal artery occlusion

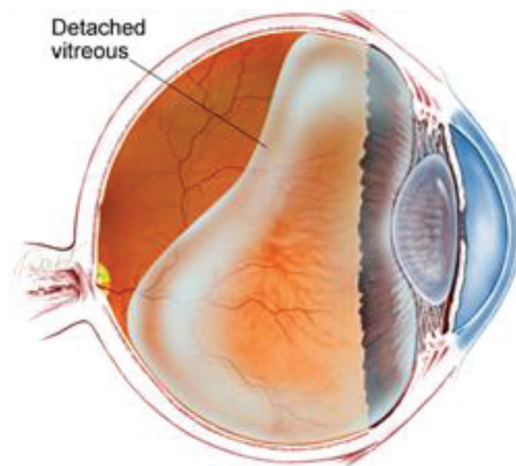
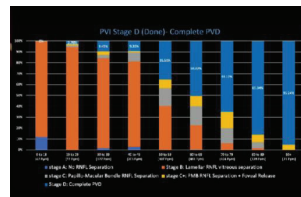
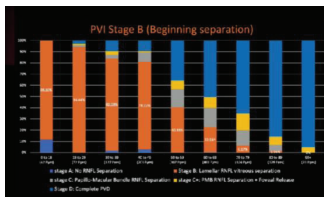
- 10-15% will develop NVI and or NVA



Mason et al. Clinical Ophthalmology 9:995-1000;2015

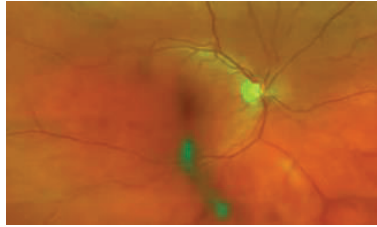
Posterior vitreous detachment

- Normal aging process
- After 40 ?



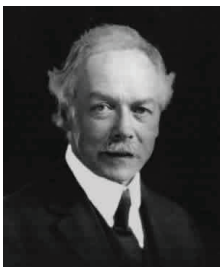
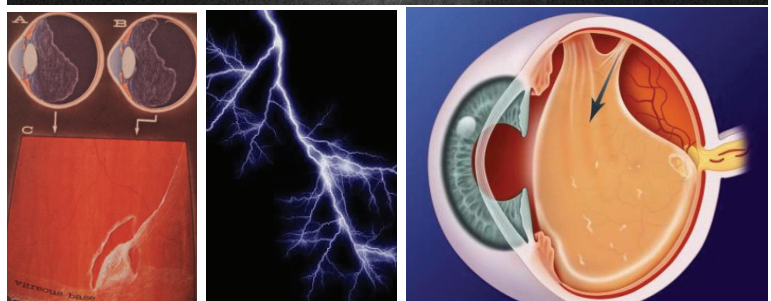
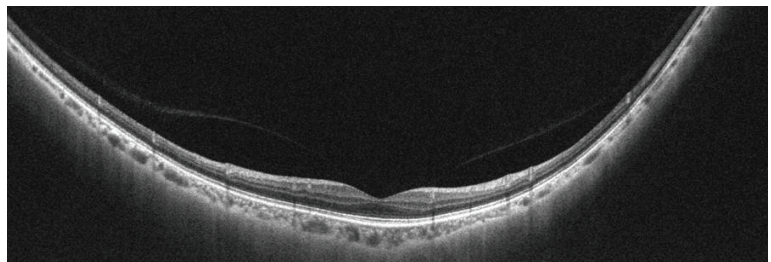
Posterior vitreous detachment

- Floaters
 - Normal phenomenon

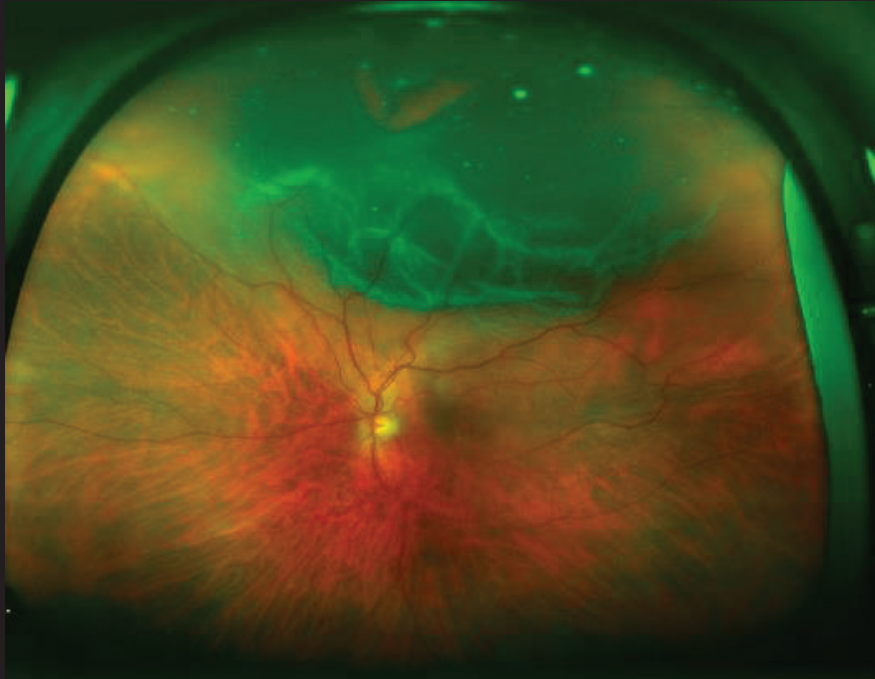


Posterior vitreous detachment

- Floaters
 - Normal phenomenon
- Flashes of light
- Retinal tear



Jules Gonin (1870-1935)



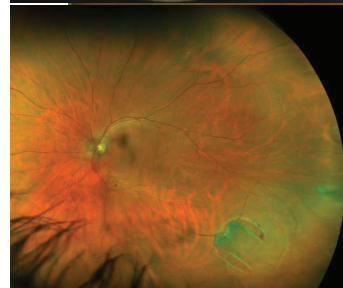
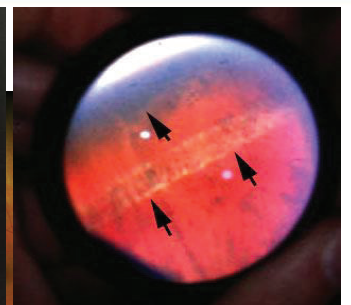
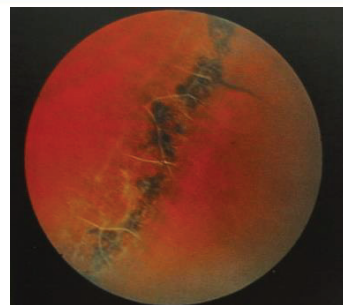
Posterior vitreous detachment

Management

- Few floaters without significant flashes
 - Good dilated exam
- Follow up in 4-6 weeks

Evaluation by retina

- Associated retinal pathology
 - Retinal tear/vitreous hemorrhage
- Significant flashes/curtain
- Unable to do a good dilated exam





Thank you

pgiuliari@omnieyeservices.com