

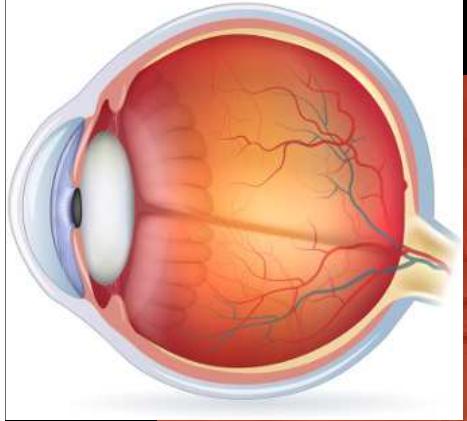


Anatomie et Physiologie de la Circulation Rétinienne

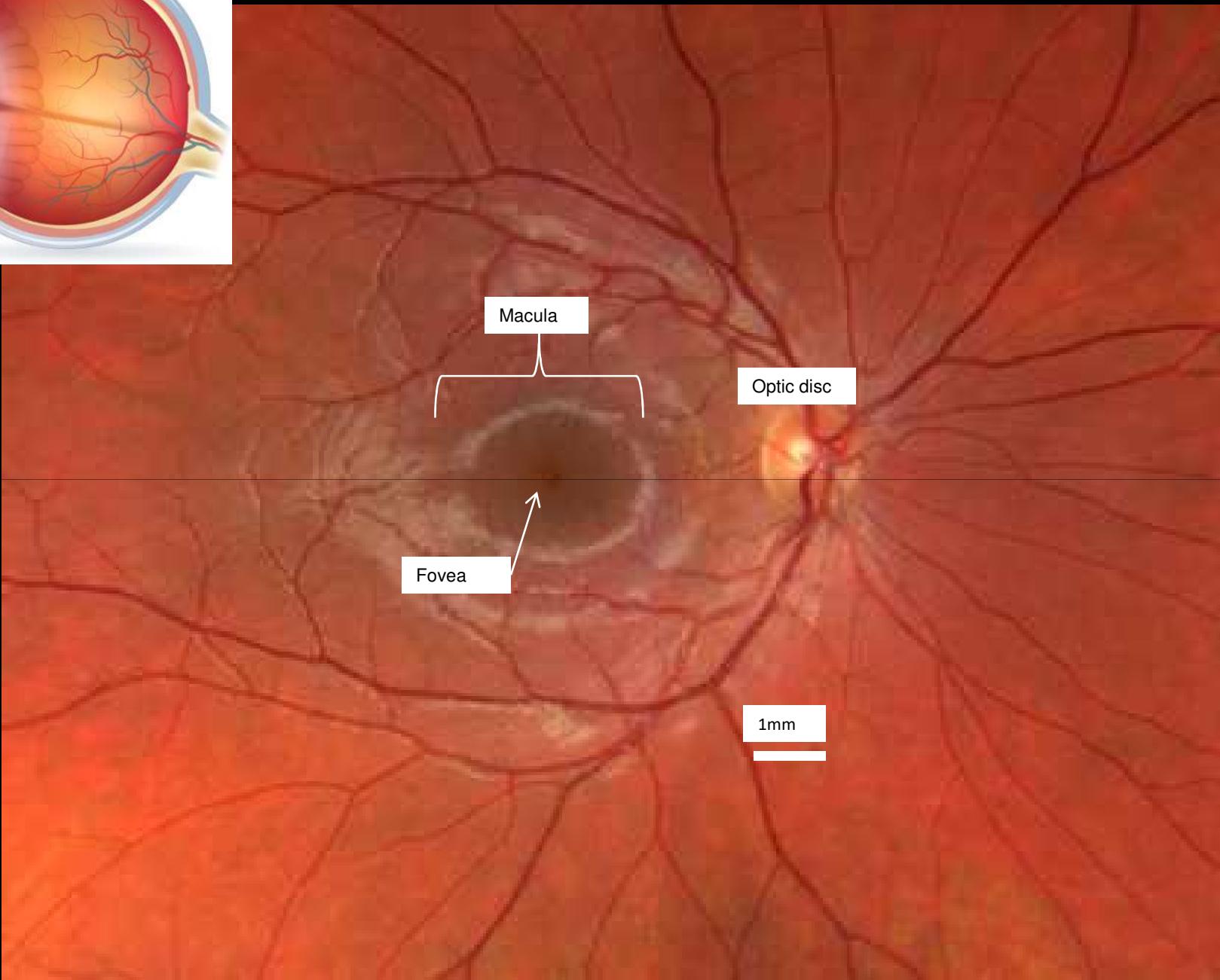
Michel Paques

CHNO des Quinze-Vingts & Institut de la Vision, Paris

aucun conflit d'intérêts

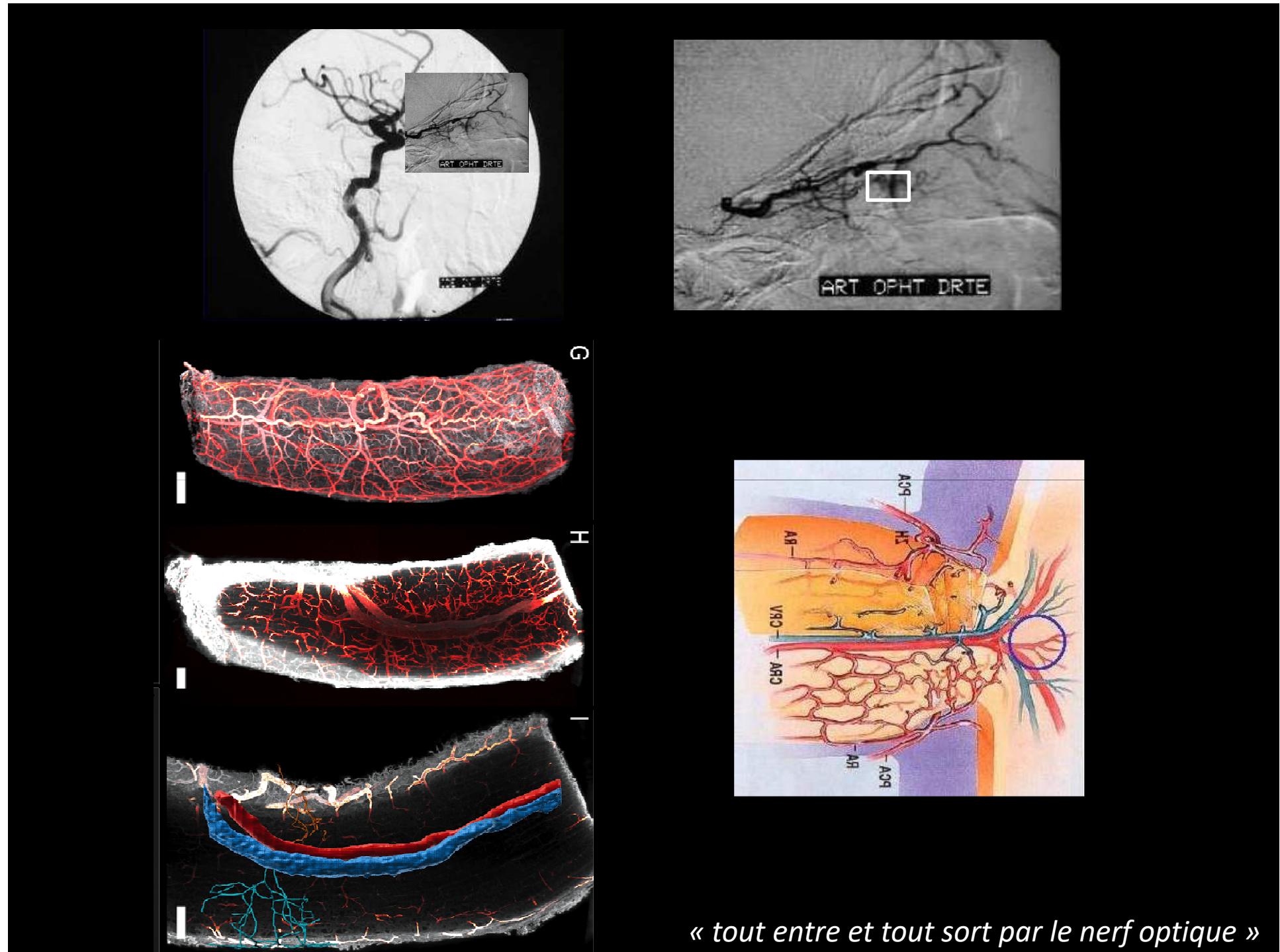


www.provisu.ch/images/en/anatomy/anatomy-of-the-eye.jpg



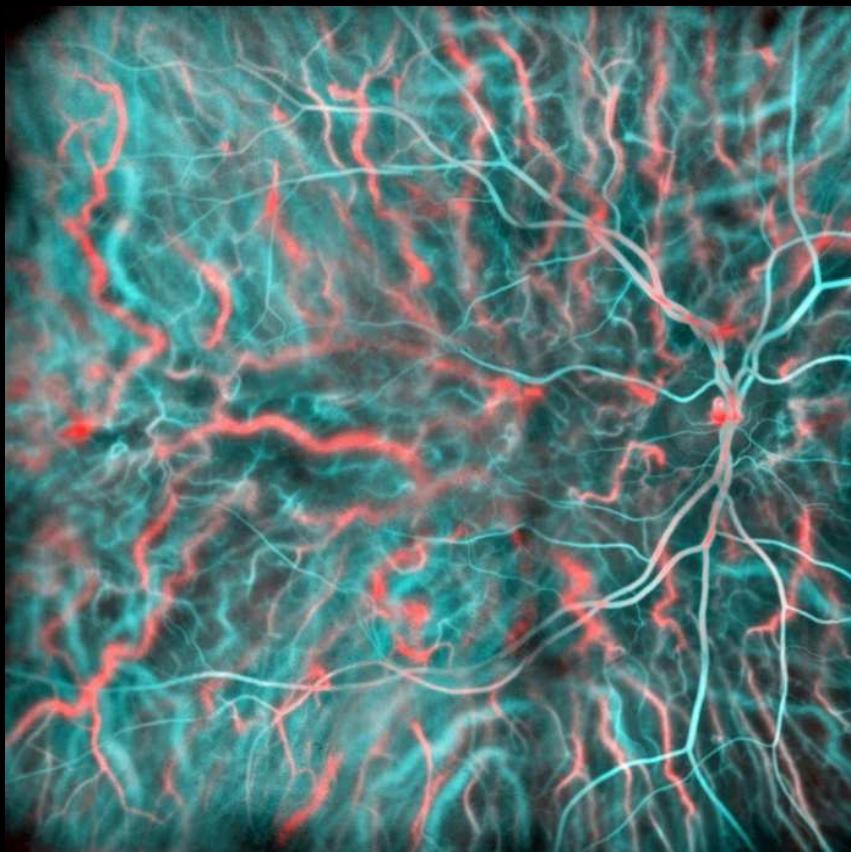


Distribution des vaisseaux rétiniens: véritable « empreinte digitale » rétinienne



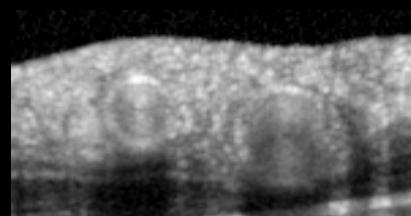
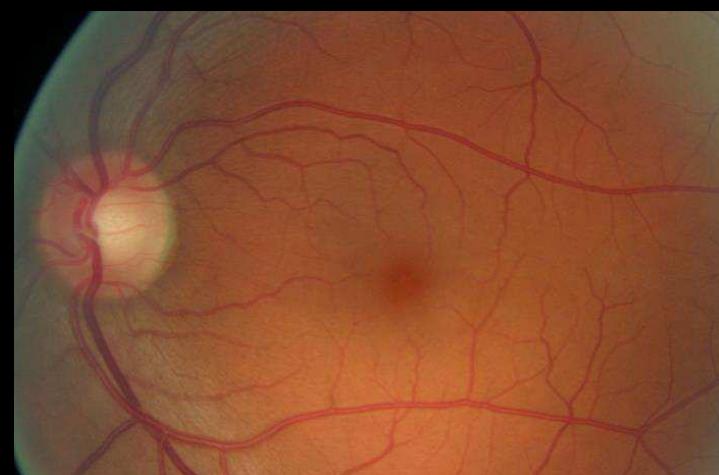
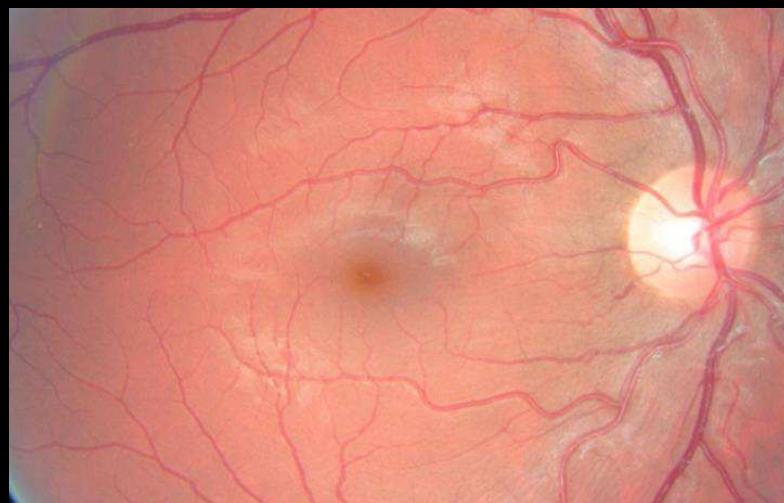
« tout entre et tout sort par le nerf optique »

Retinal blood flow is one order of magnitude
inferior to the choroidal flow



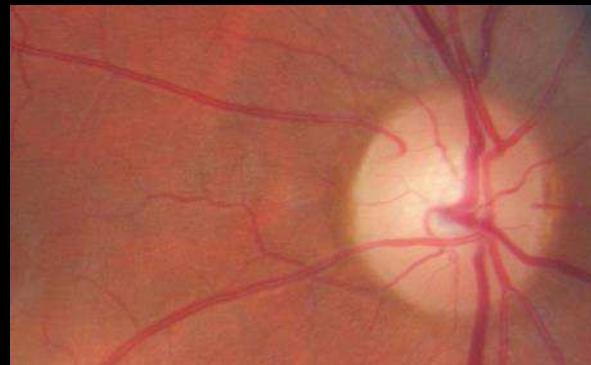
Principes généraux de l'organisation vasculaire rétinienne:

- L'artère centrale est en nasal de la veine centrale
- Artères et veines alternent autour du nerf optique
- Les vaisseaux sont plutôt rectilignes, sauf autour du pôle postérieur
- Les vaisseaux tendent à former des paires artéioveineuses
- Une artère ne croise pas une artère; idem pour les veines
- Les artères sont plutôt plus proches de la surface rétinienne que les veines
- Deux artères encadrent la macula



Les cas particuliers

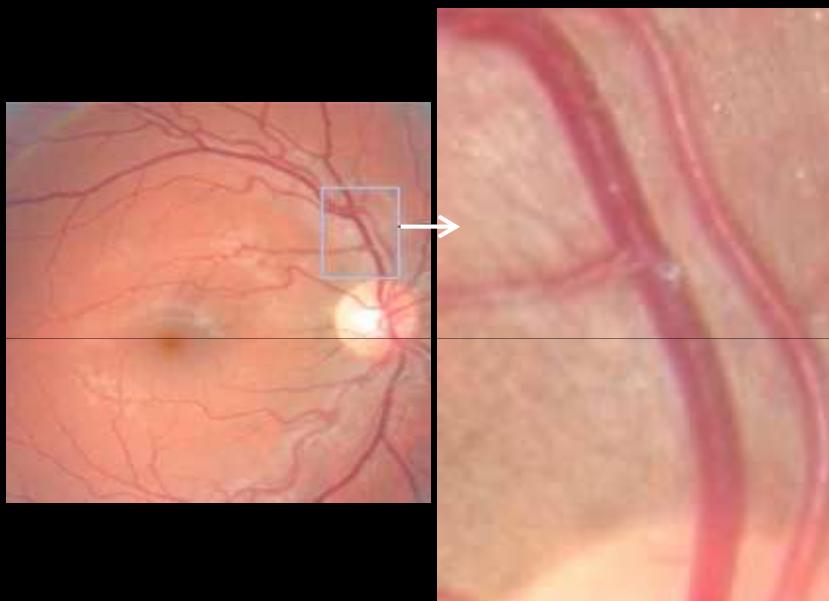
- Artères ciliorétinienne ($\sim 20\%$)
 - *Les veines ciliorétiniennes n'existent pas (sauf après une occlusion veineuse)*

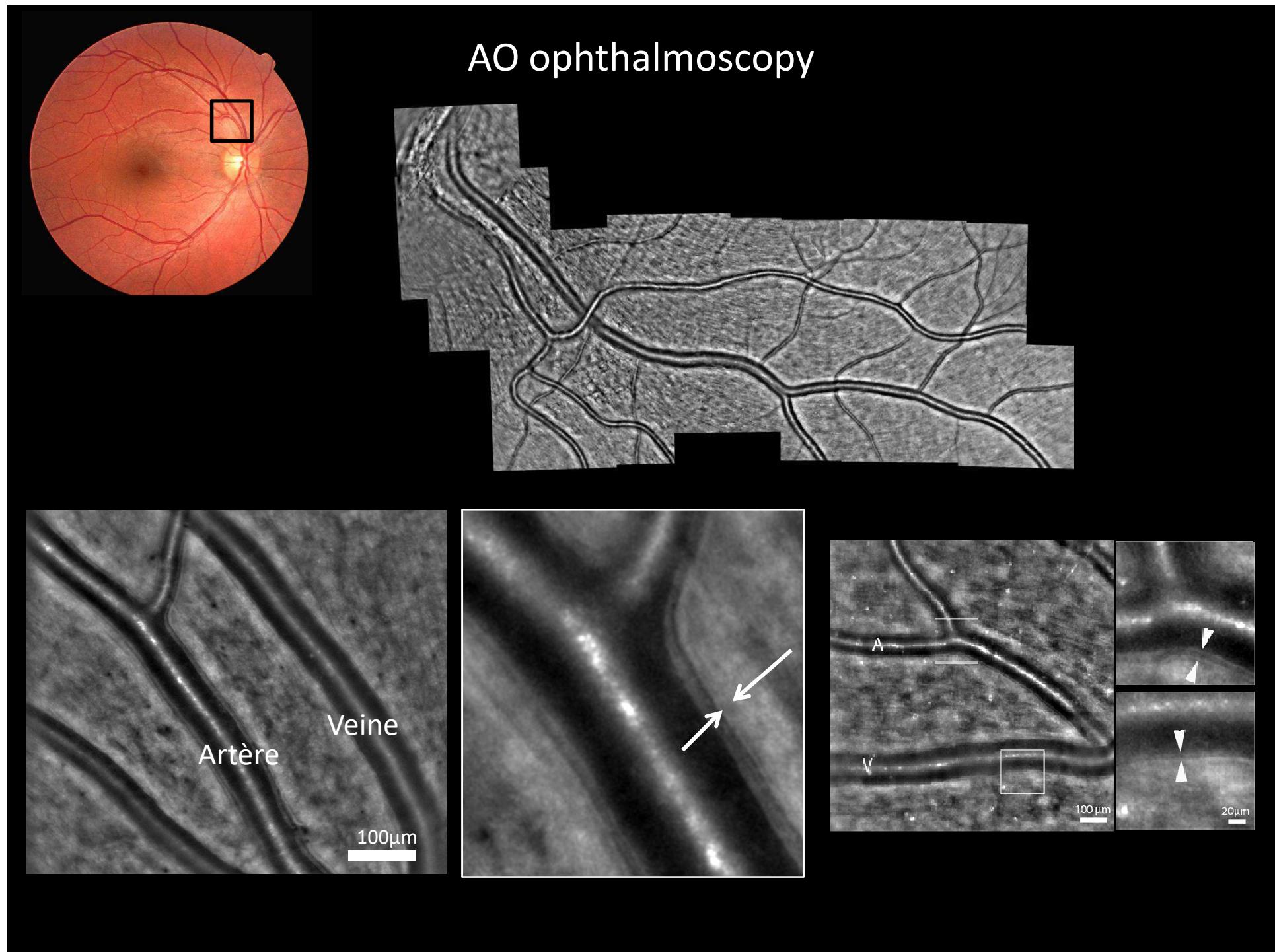


- La duplication du tronc de la veine centrale n'est pas rare ($\sim 20\%$)

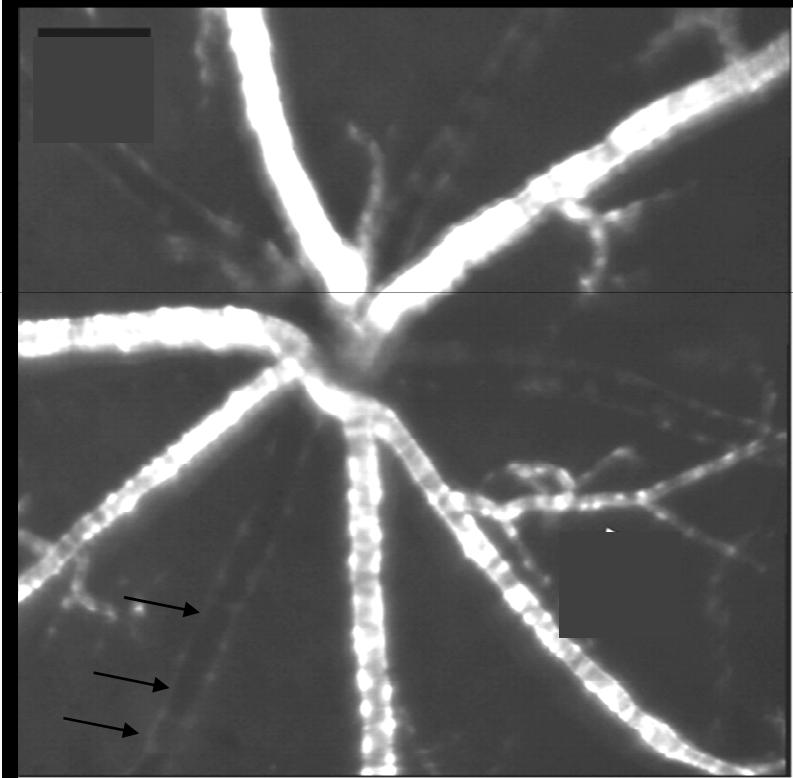
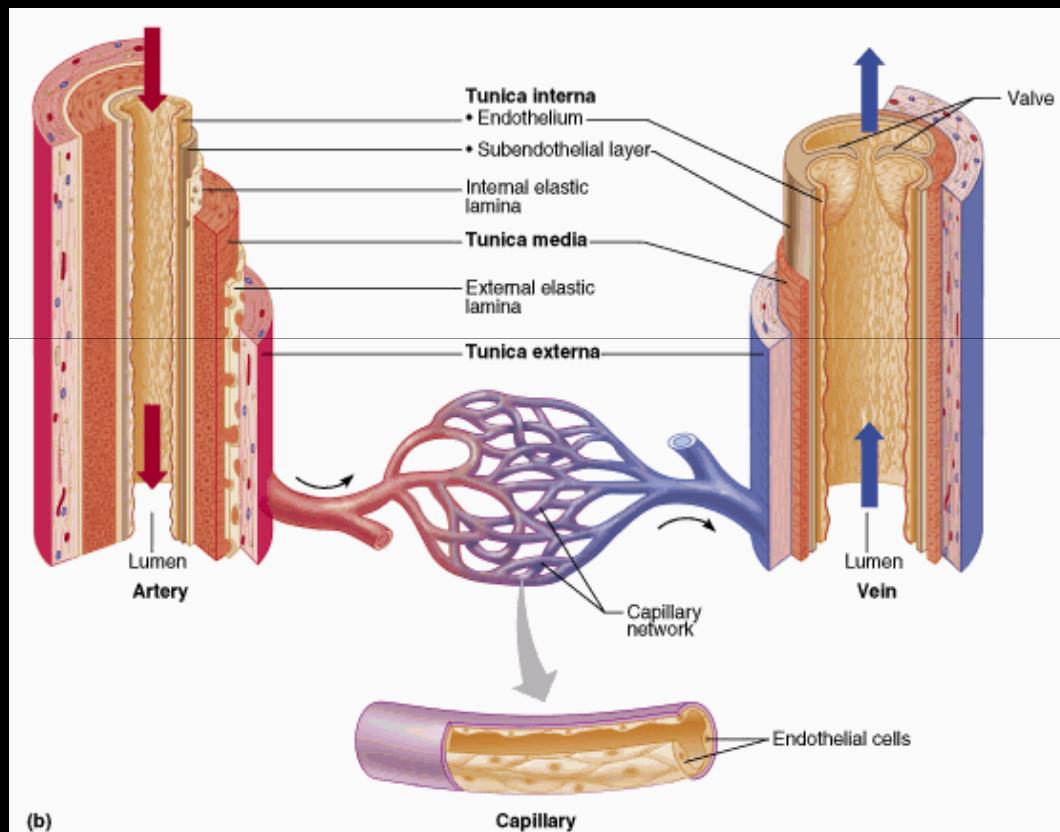


Only adaptive optics ophtrhalmoscopy enables to observe the vessel itself

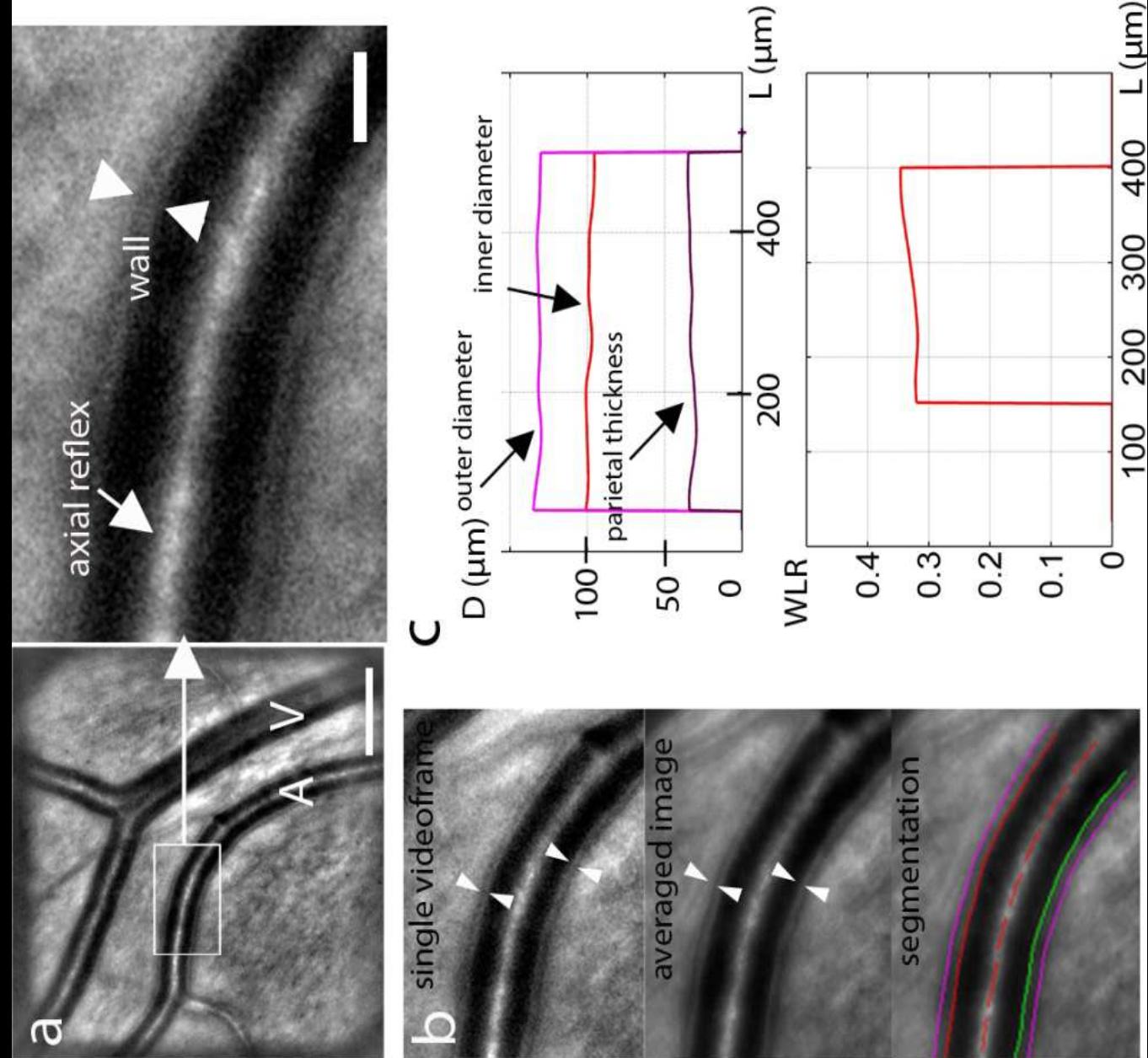


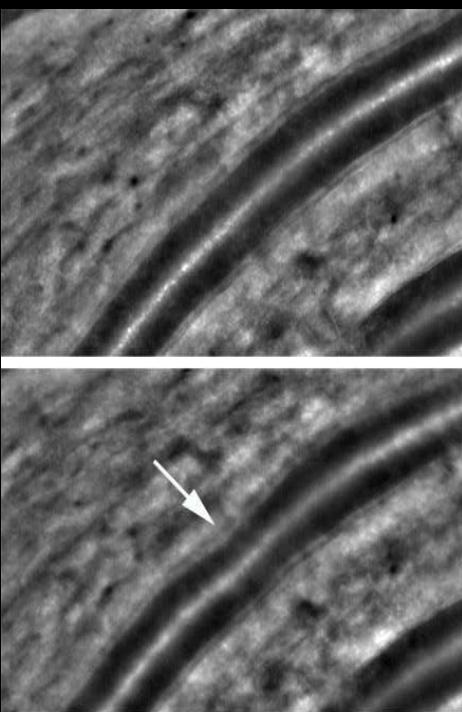
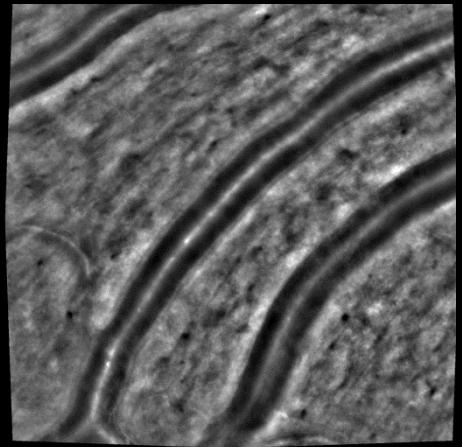
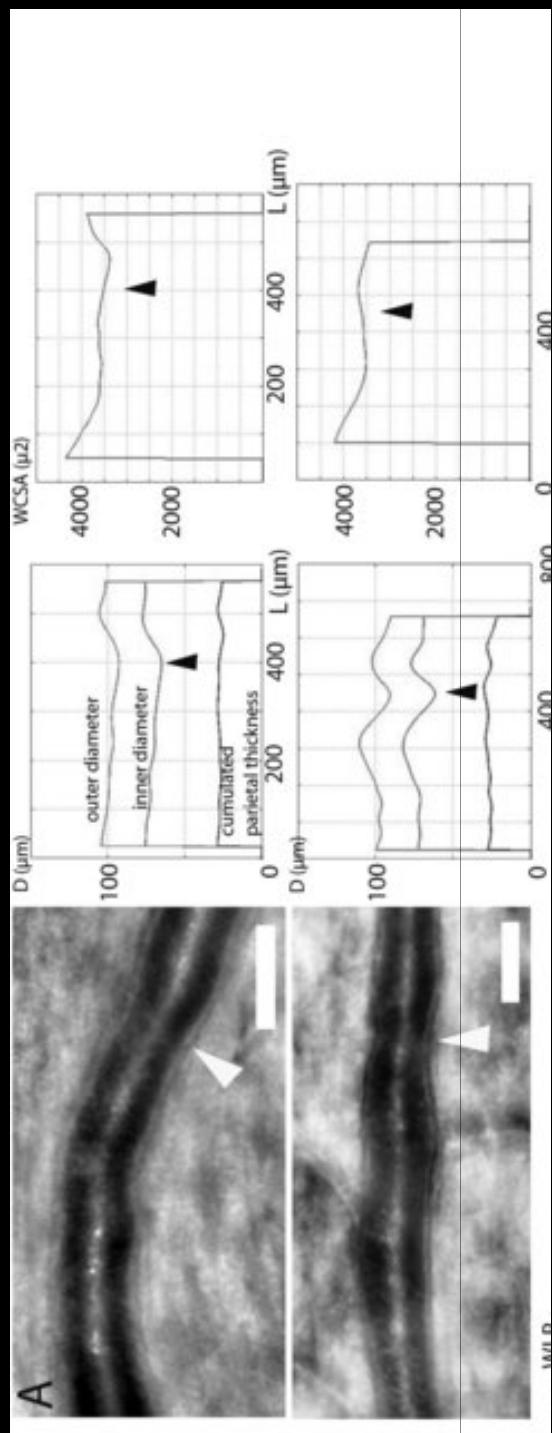


What's in a vessel wall?



Ficher et al. IOVS 2010





$\text{WLR} = 0.0051 + 0.0025 \cdot \text{mean pressure} + 0.0014 \cdot \text{age}$ which accounts for 43% of the variability of the WLR

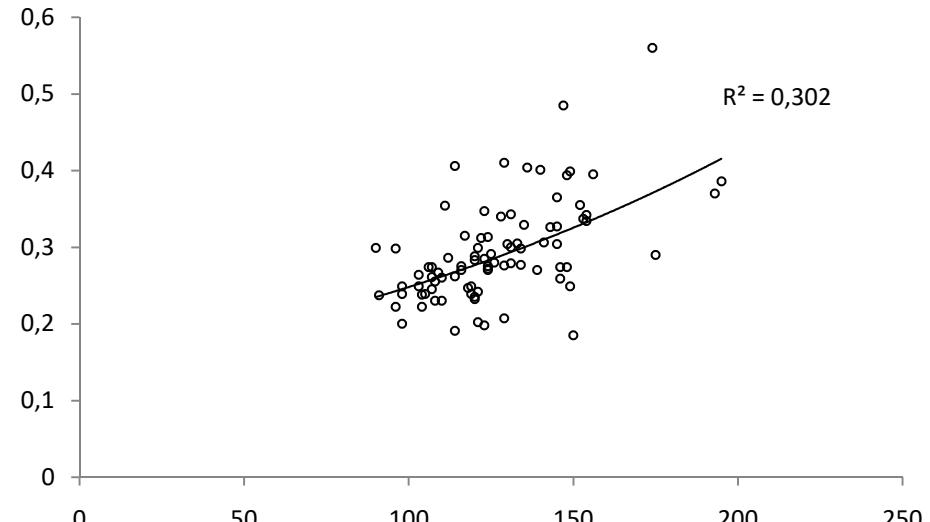
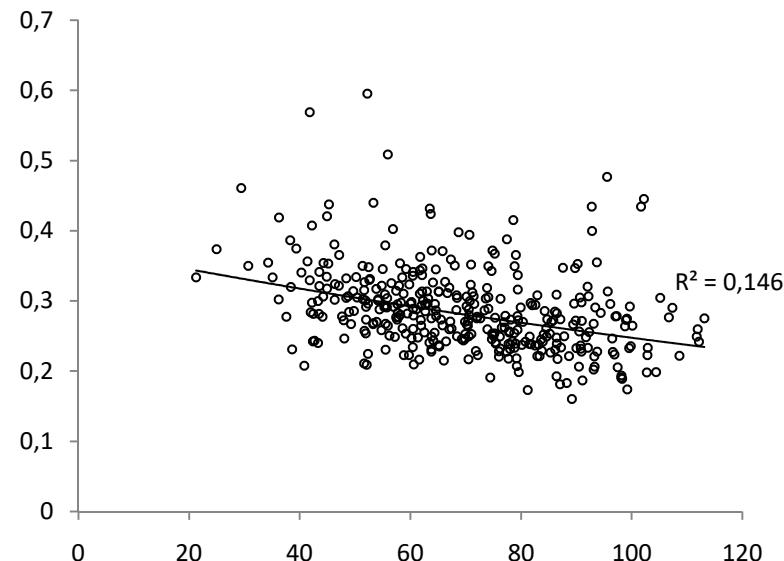
	D	P	WLR	WCSA
Age	-0.173	0.331*	0.348*	0.183
BMI	-0.254	0.241*	0.342*	0
SBP	-0.384**	0.438*	0.582**	0.13
DBP	-0.362*	0.437*	0.559**	0.06
Mean BP	-0.385**	0.453*	0.589**	0.05
Pulse pressure	-0.275	0.283	0.406**	0.01

D, diameter; P, parietal thickness; WCSA, wall cross-sectional area; WLR, wall-to-lumen ratio.

* $P < 0.05$.

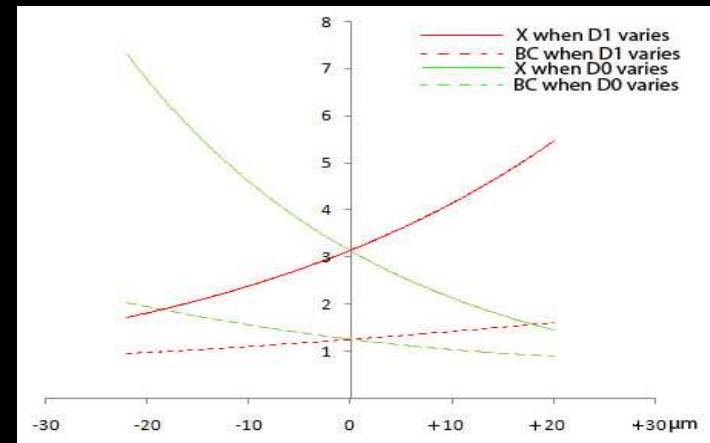
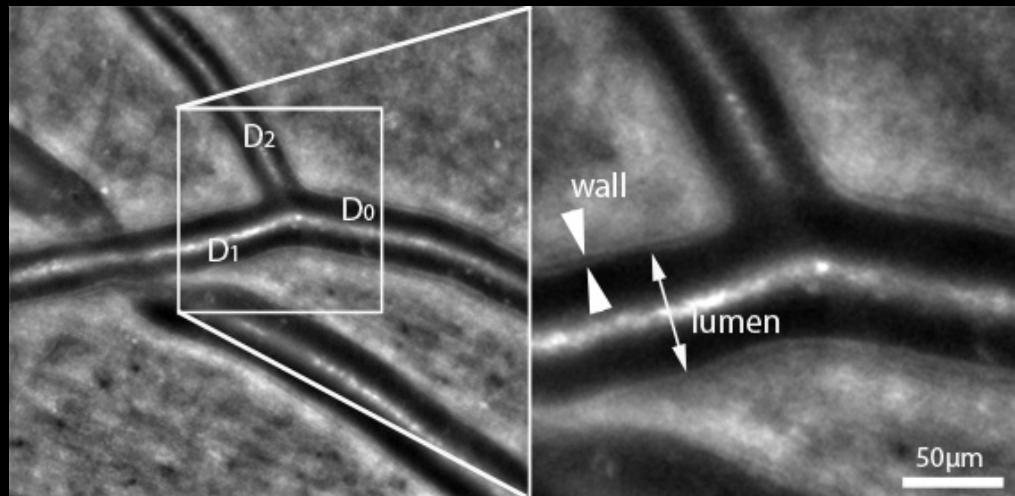
** $P < 0.01$.

Koch et al J Hypertens 2014

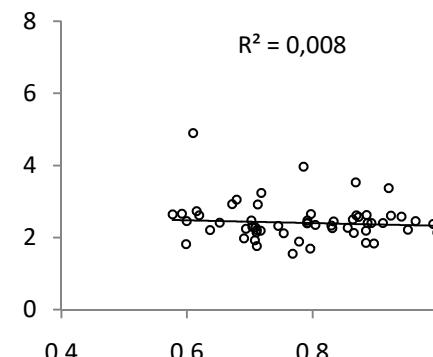
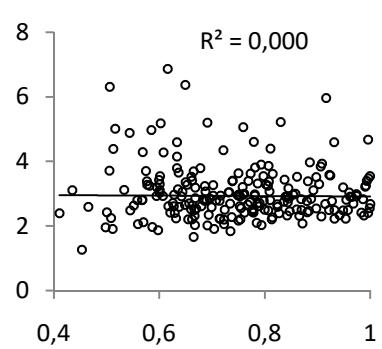


WLR depends on the size of the vessel... and on BP

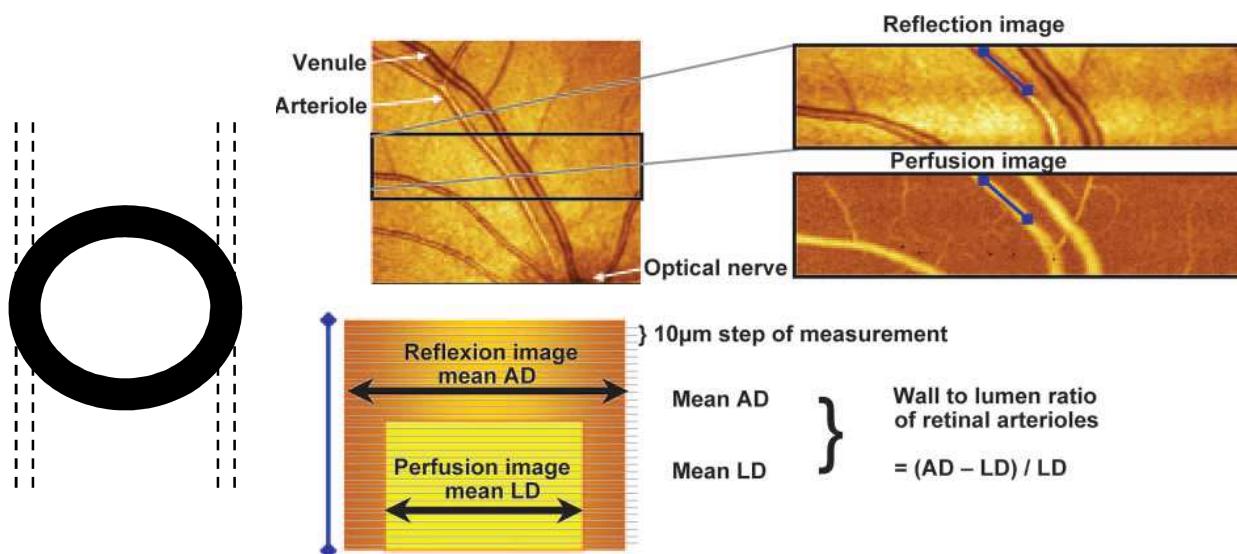
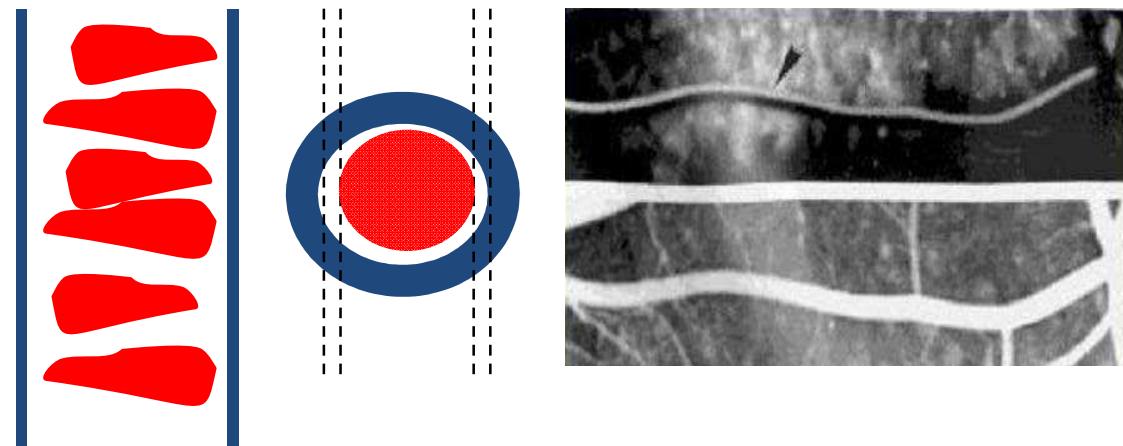
Vascular morphometry: Murray's law



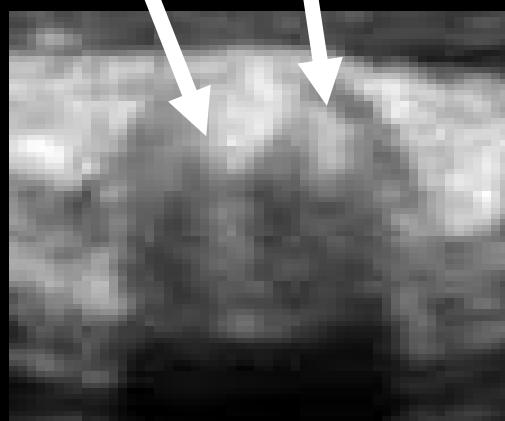
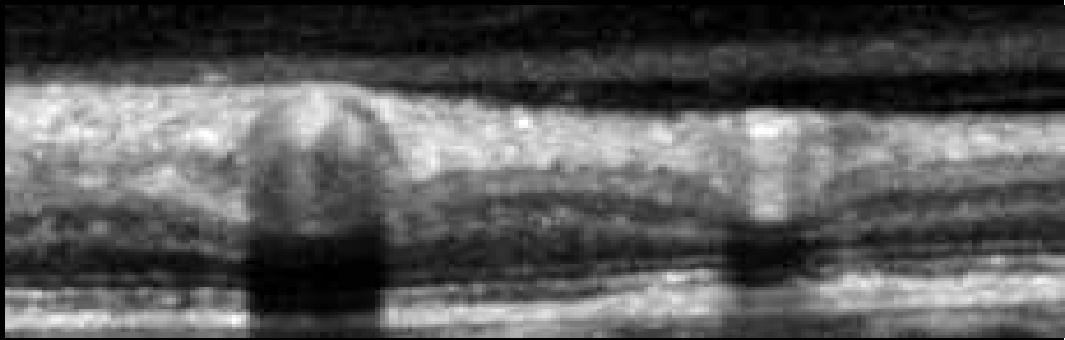
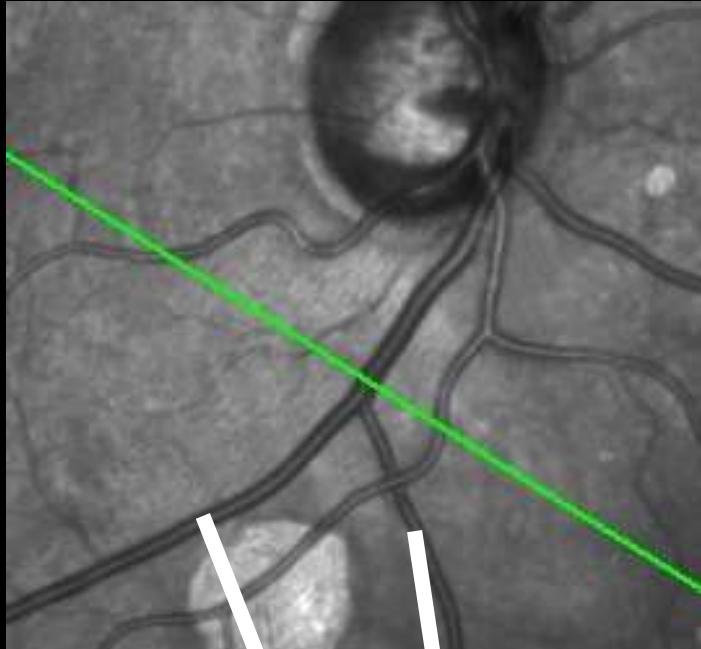
	Arteries (n= 227)	Veins (n=58)
Lumen diameter (μm)	D_0 83.3 (± 14) D_1 73.1 (± 14.1) D_2 53.9 (± 11)	D_0 112.6 (± 19.7) D_1 93.6 (± 19.4) D_2 72.4 (± 14.3)
WLR	D_0 0.274 (± 0.05) D_1 0.281 (± 0.06) D_2 0.334 (± 0.08)	N/A
X	3.03 (± 0.83)	2.46 (± 0.55)



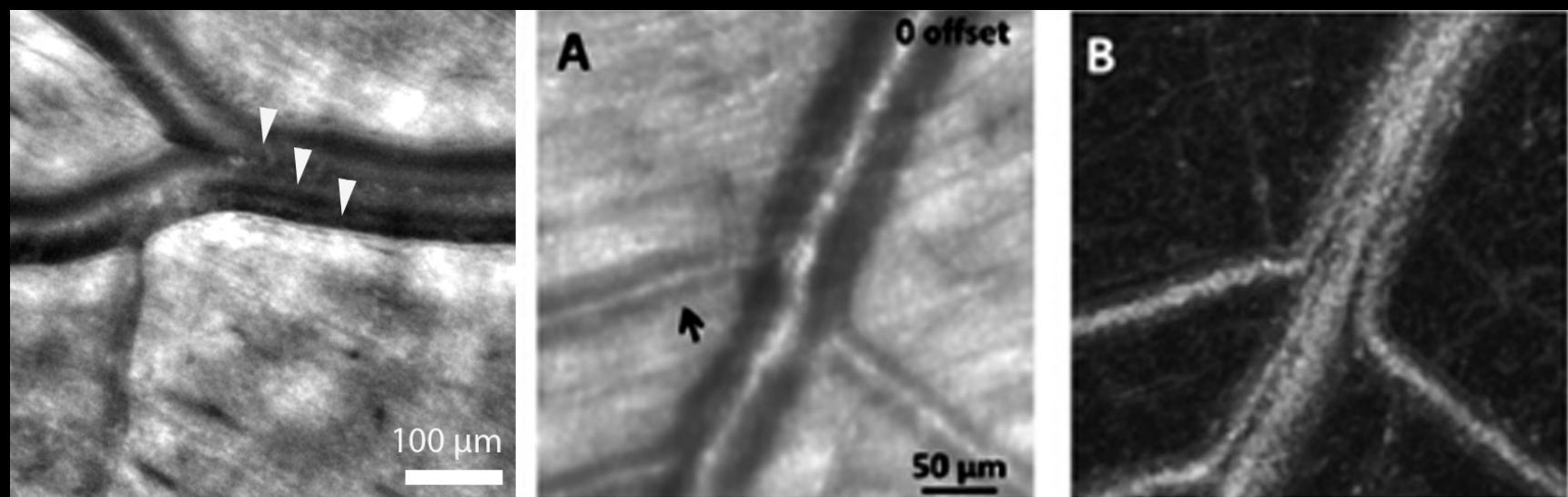
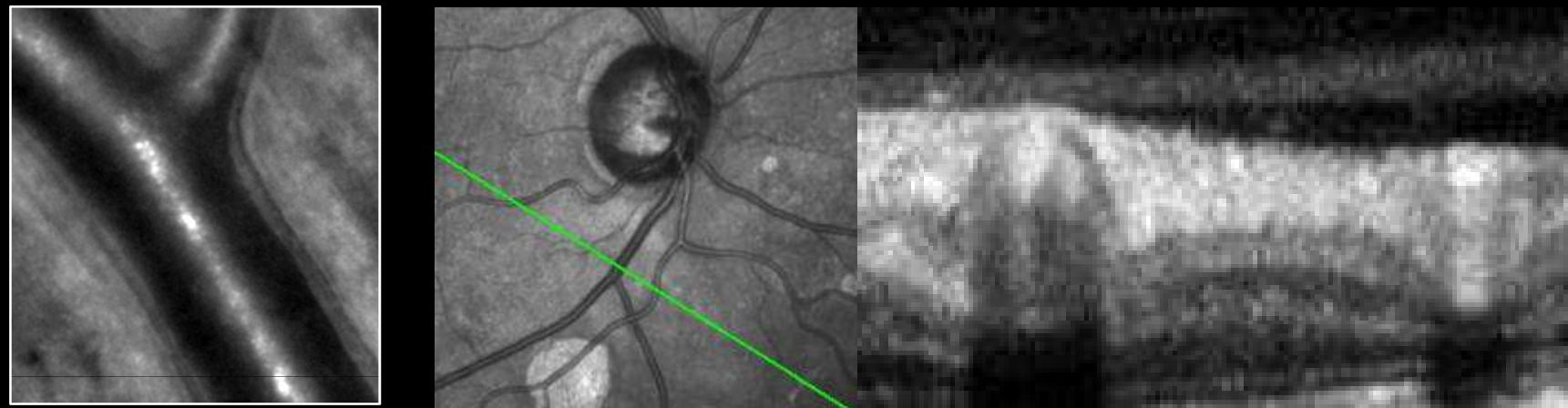
What's in the lumen?



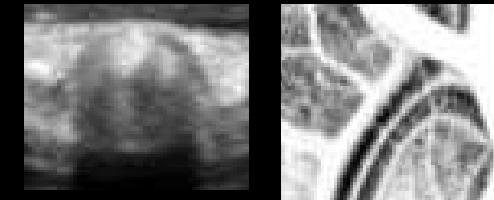
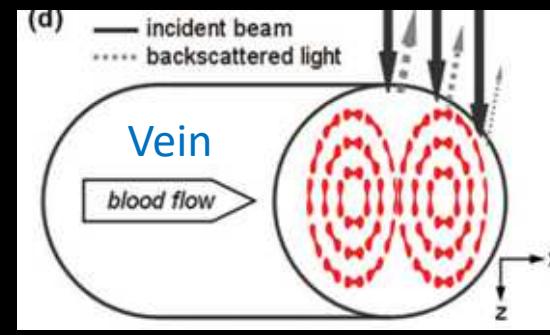
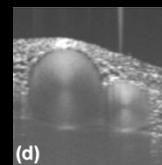
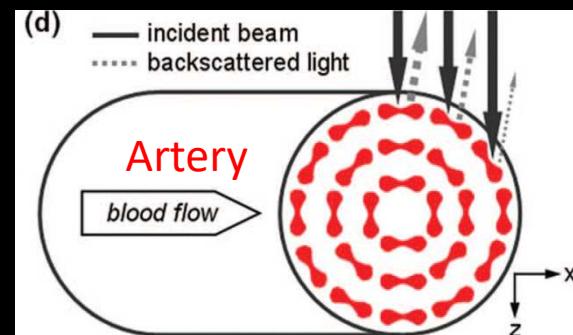
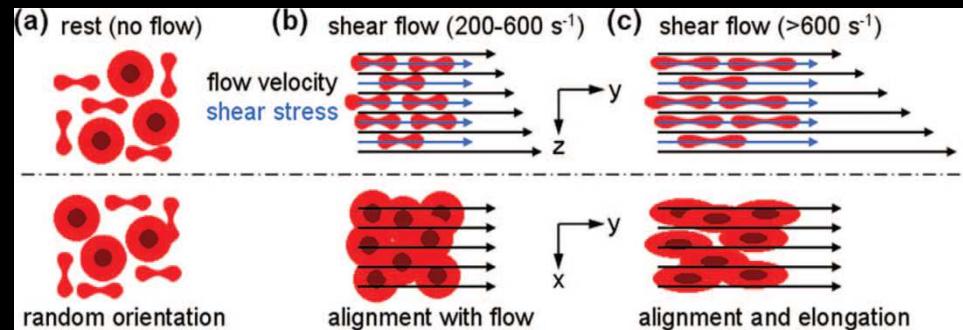
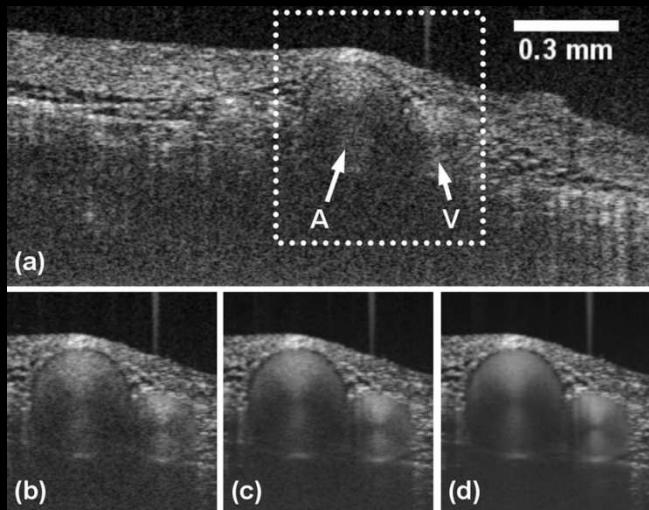
Venous flow is not organized the same was as arterial flow



Organisation du flux sanguin veineux en lamelles parallèles



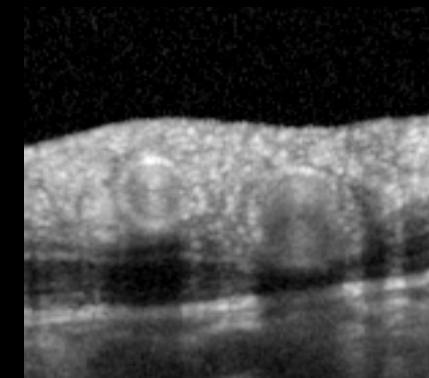
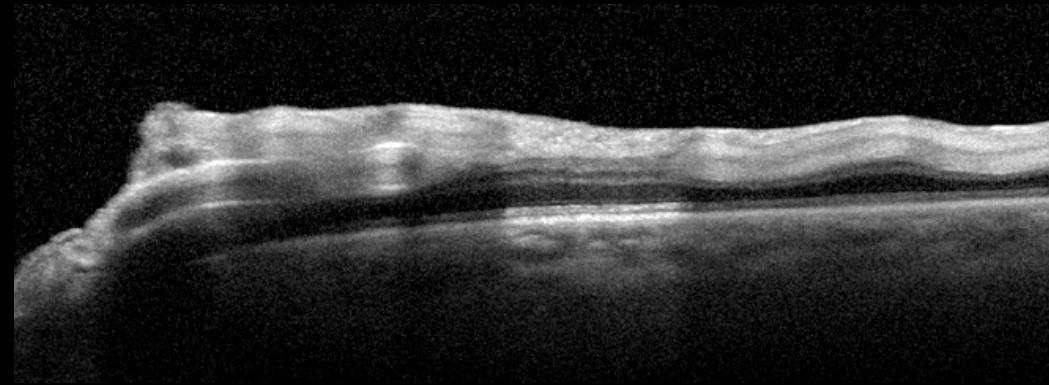
OCT imaging of lumen reveals the organization of red cells



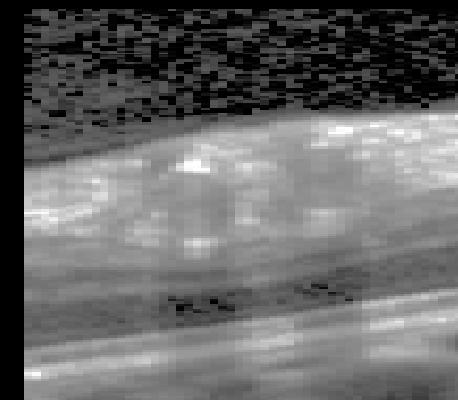
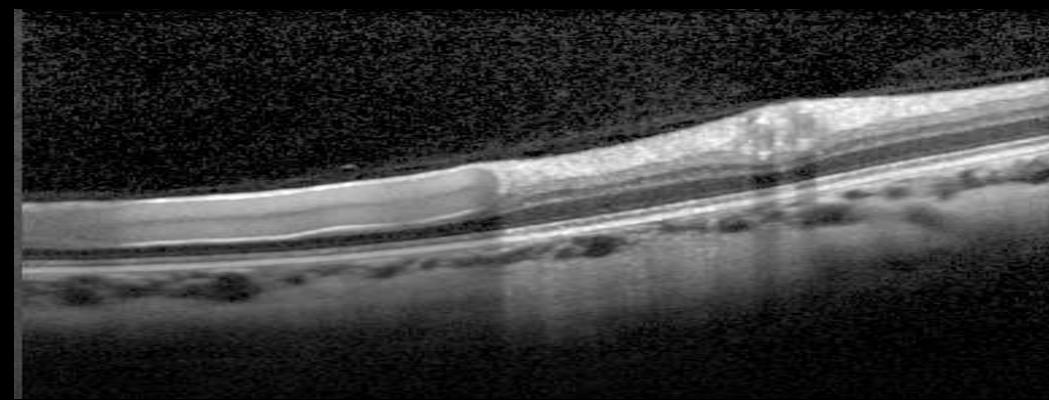
- Cimalla P, Walther J, Mittasch M, Koch E. Shear flow-induced optical inhomogeneity of blood assessed *in vivo* and *in vitro* by spectral domain optical coherence tomography in the $1.3 \mu\text{m}$ wavelength range. *J Biomed Opt.* 2011 Nov;16(11):116020.

L'anémie atténue la réflexion intraluminale

normal



anémie

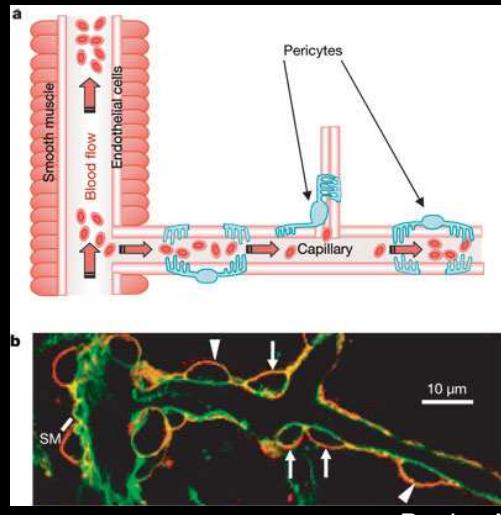
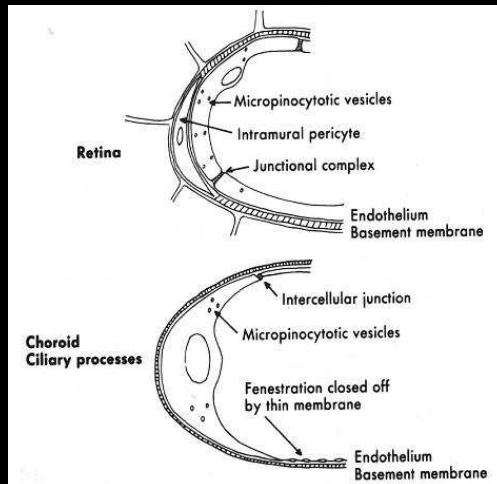


→ la présence des globules rouges est responsable de l'aspect en « diabolo » en OCT

Structure and organization of retinal capillaries

Unité capillaire rétinienne: cellules endothéliales et péricytes

- Diamètre 5 à 7 µm
- Barrière hématorétinienne interne
- Importante couverture péricyttaire (ratio péricyte / cellule endothéliale 1/1)
- Réseau de communication entre péricytes (nanotubes)?



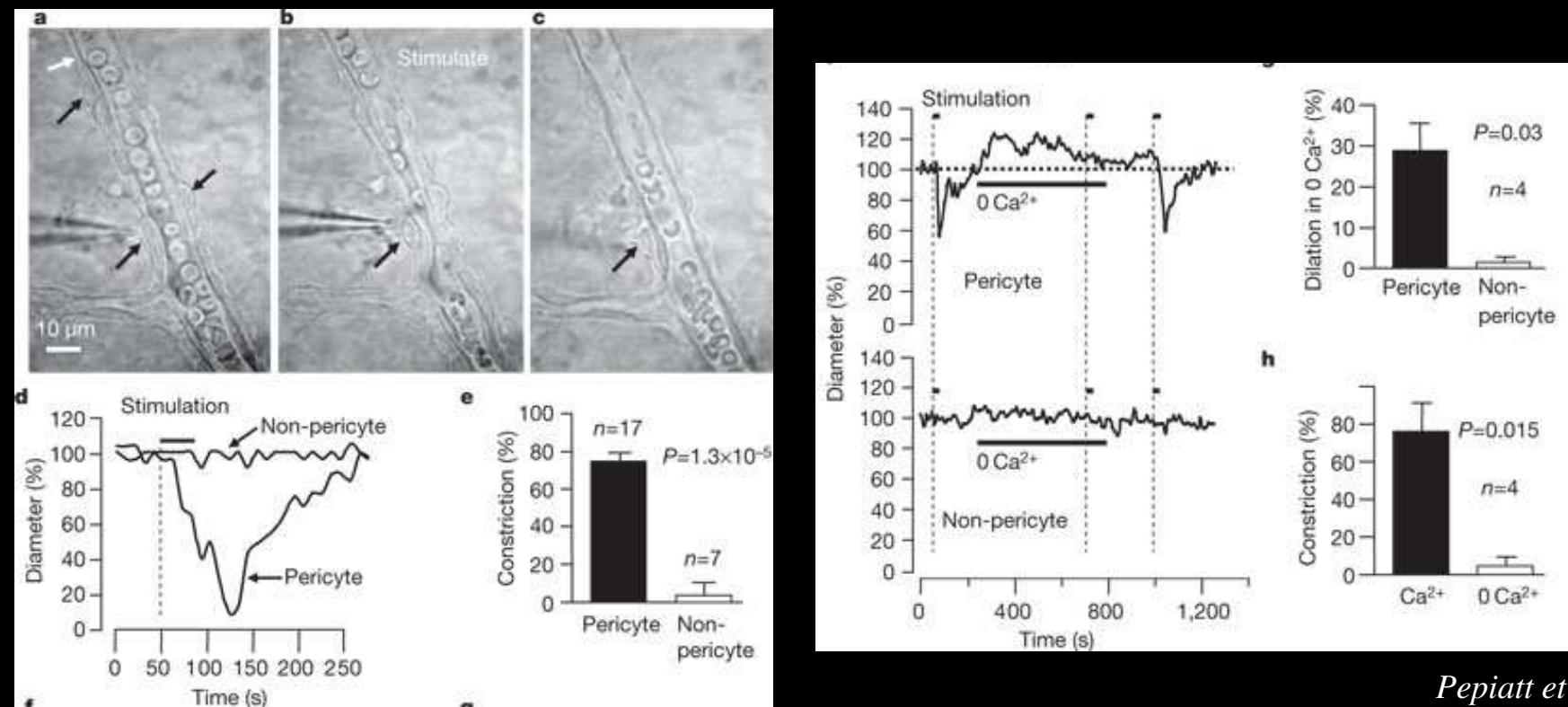
Pepiatt *Nature* 2006



Pericyte dysfunction and loss of interpericyte tunneling nanotubes promote neurovascular deficits in glaucoma

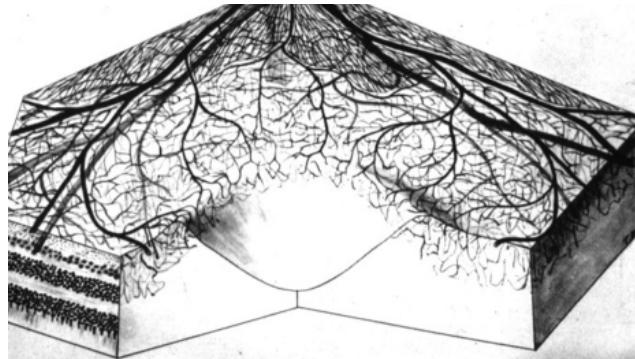
Luis Alarcon-Martinez^{a,b,1,2,3}, Yukihiko Shiga^{a,b,1}, Deborah Villafranca-Baughman^{a,b}, Nicolas Belforte^{a,b}, Heberto Quintero^{a,b}, Florence Dotigny^{a,b}, Jorge L. Cueva Vargas^{a,b}, and Adriana Di Polo^{a,b,2}

Pericyte (probably) control capillary flow

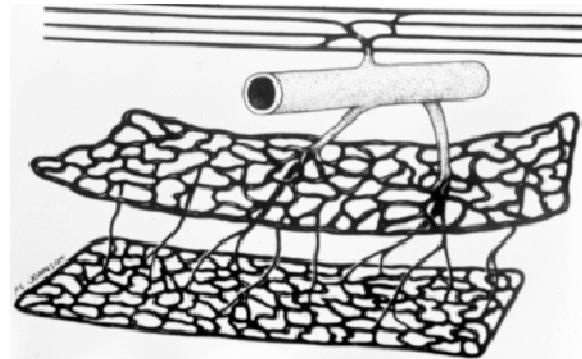


Pepiatt et coll
Nature 2006

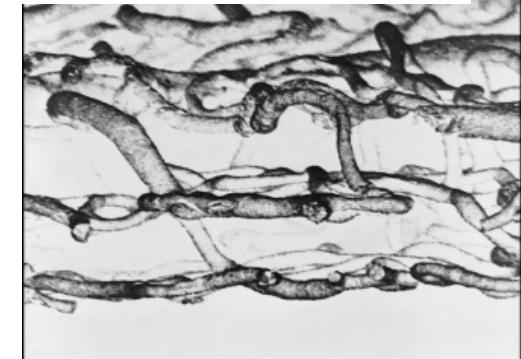
There is no consensual model of the human capillary organization



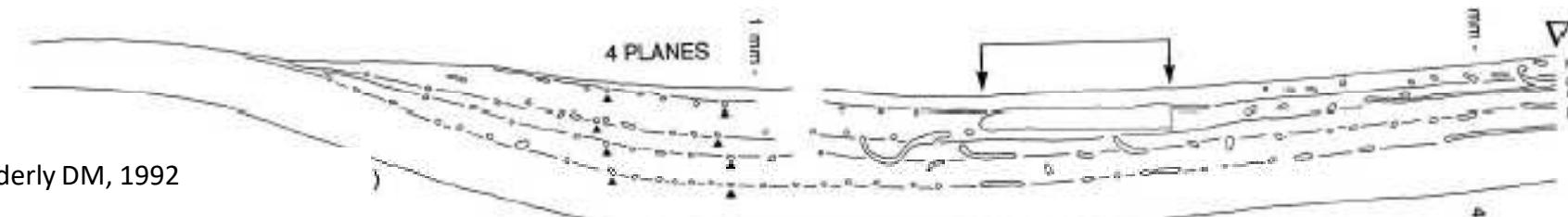
Toussaint D, 1961



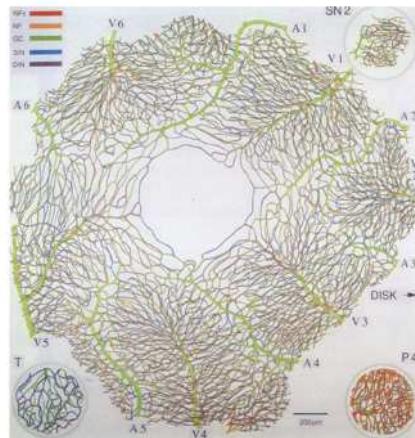
Henkind P, 1969



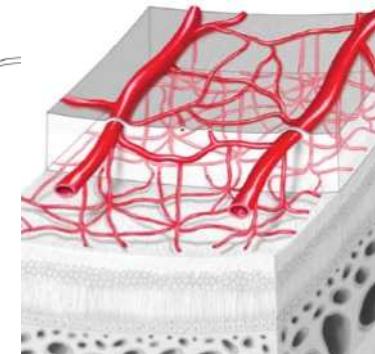
Shimizu K, 1978



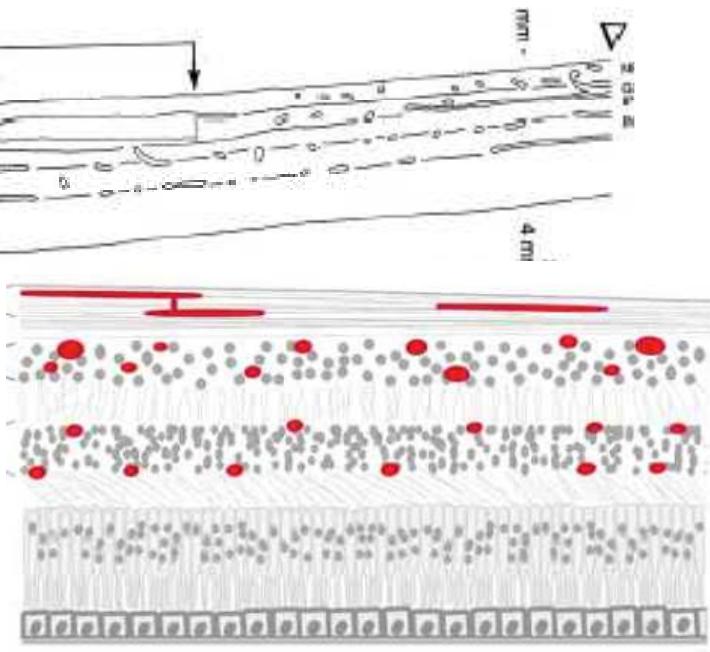
Snodderly DM, 1992



Paques M, 2003



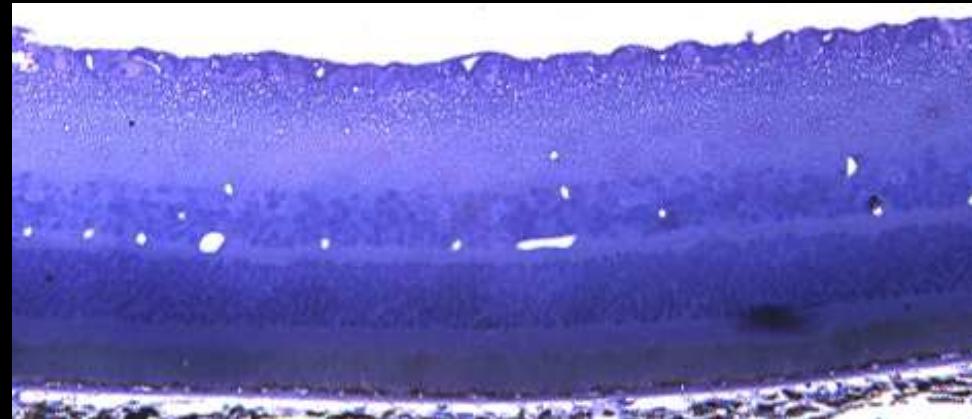
Lumbroso B, 2015



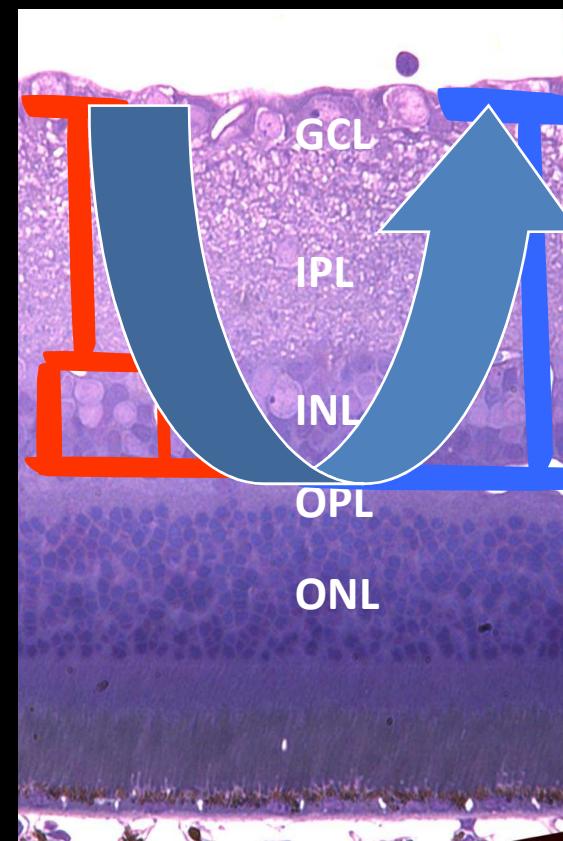
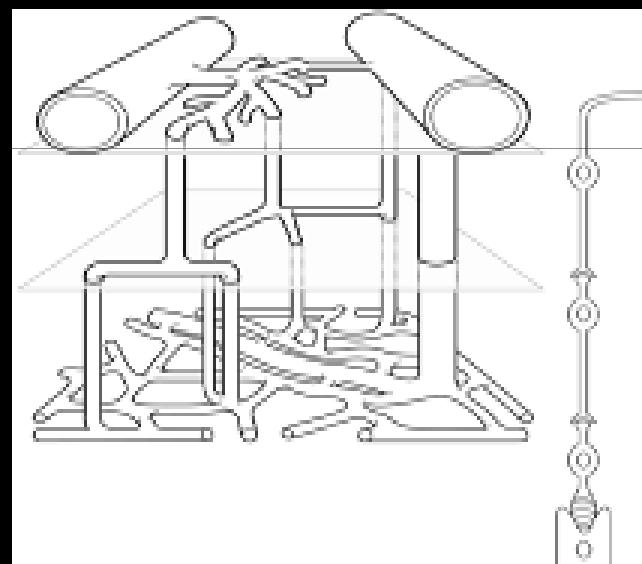
Spaide R, 2015

OCT Angiography gives , for the first time the possibility to study in vivo the 3D architecture of the retinal capillary network.

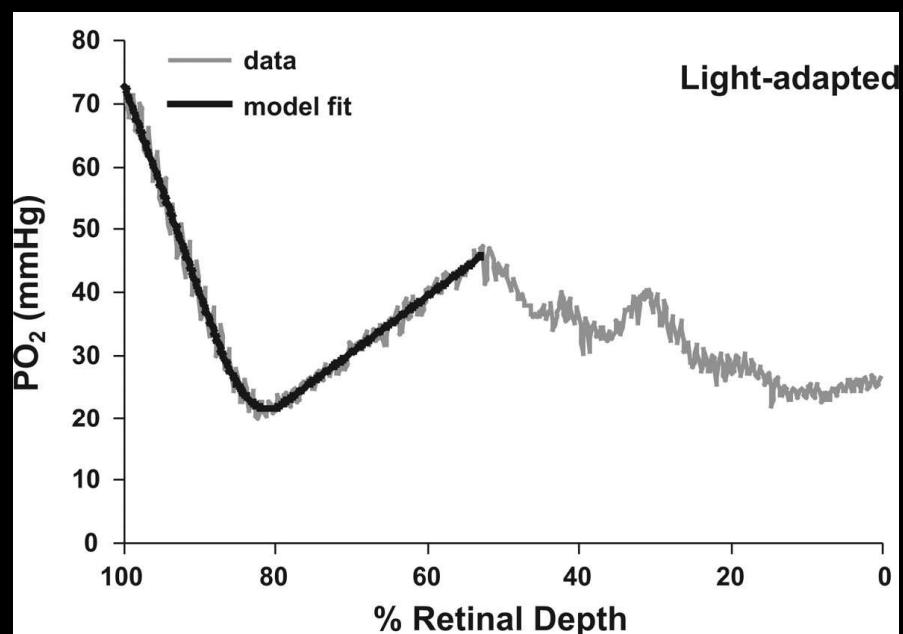
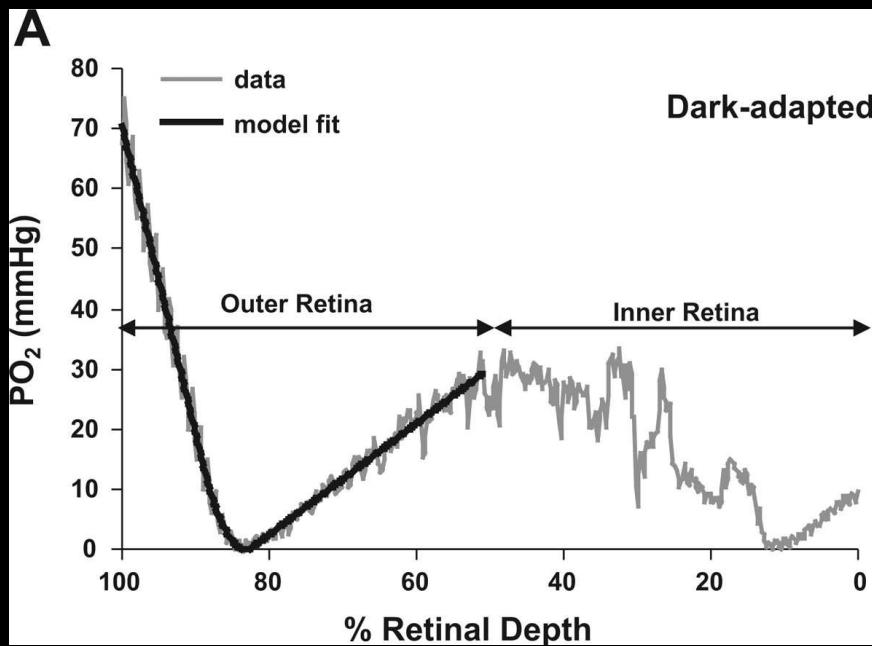
Seule la rétine interne est perfusée par les vaisseaux rétiens



Inner plexus
Intermediary plexus
Outer plexus

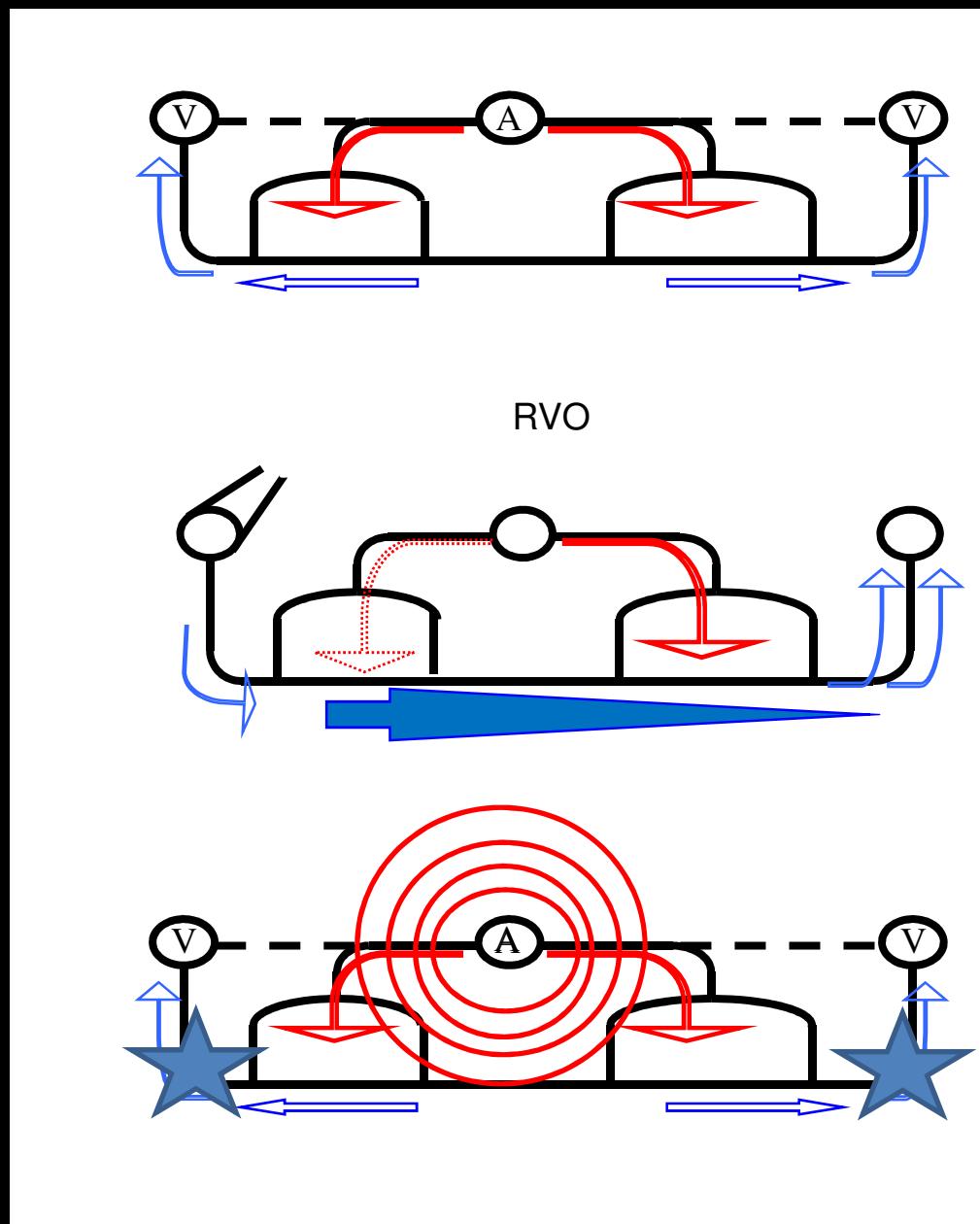
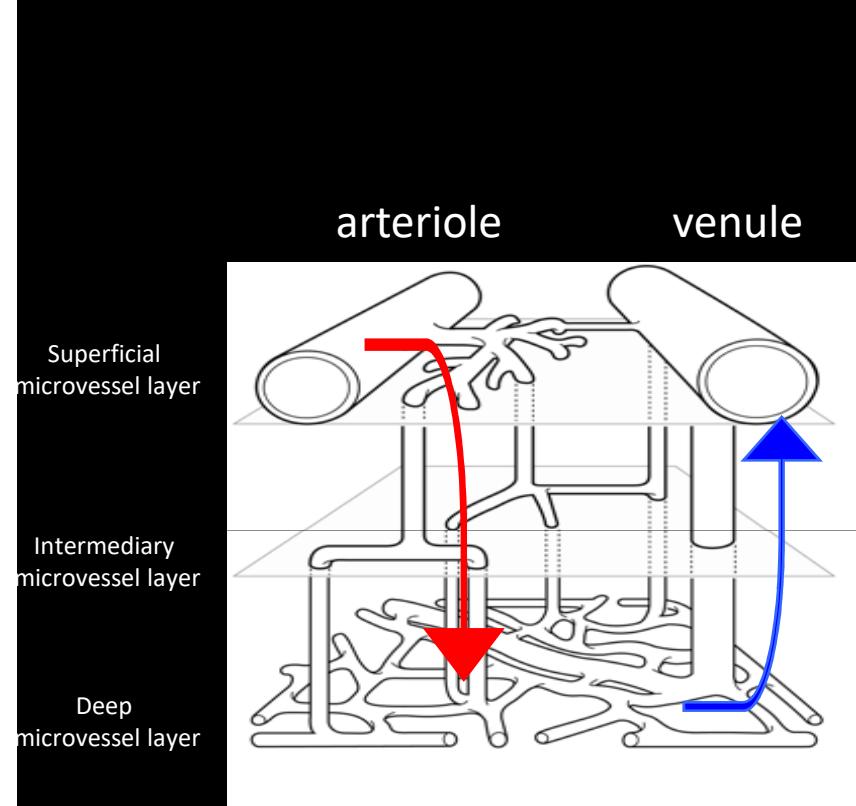


La demande en oxygène augmente à l'obscurité



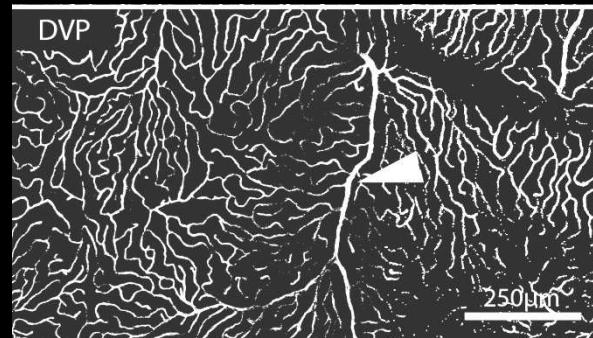
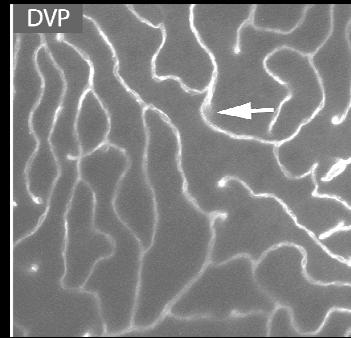
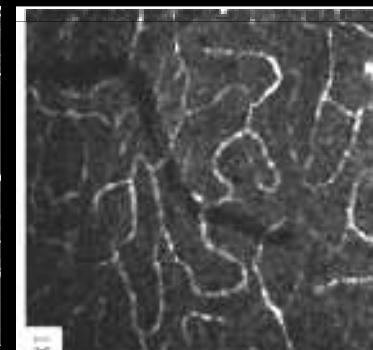
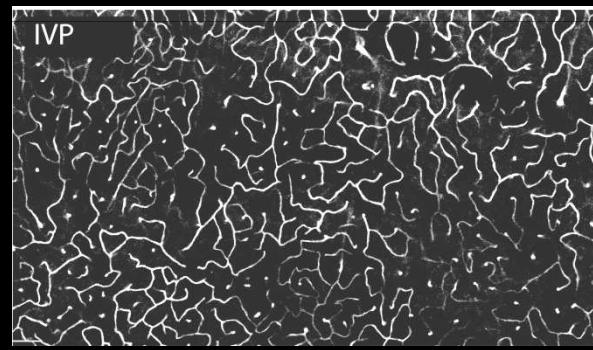
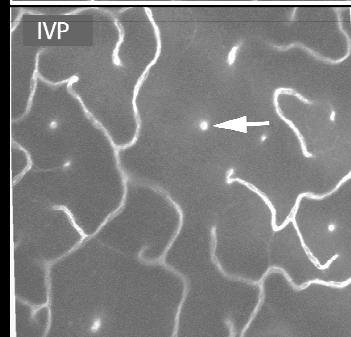
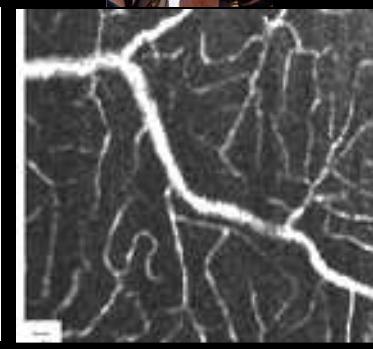
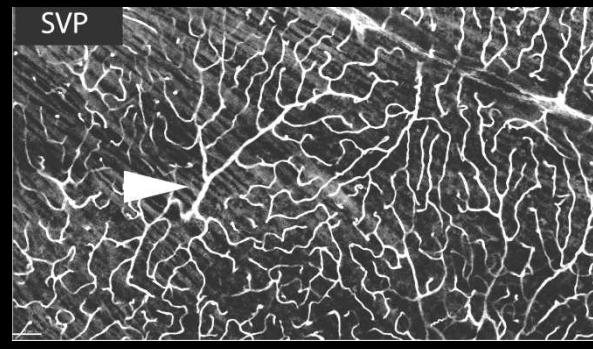
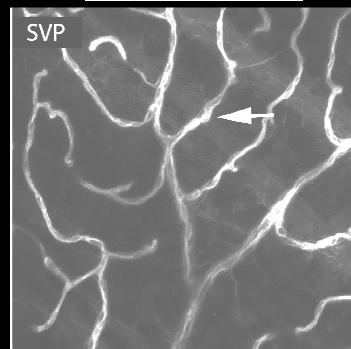
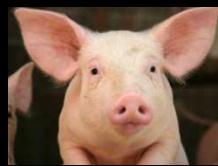
Birol, G. et al. Am J Physiol Heart Circ Physiol 293: H1696-H1704 2007

What does this model tells us about vascular diseases?

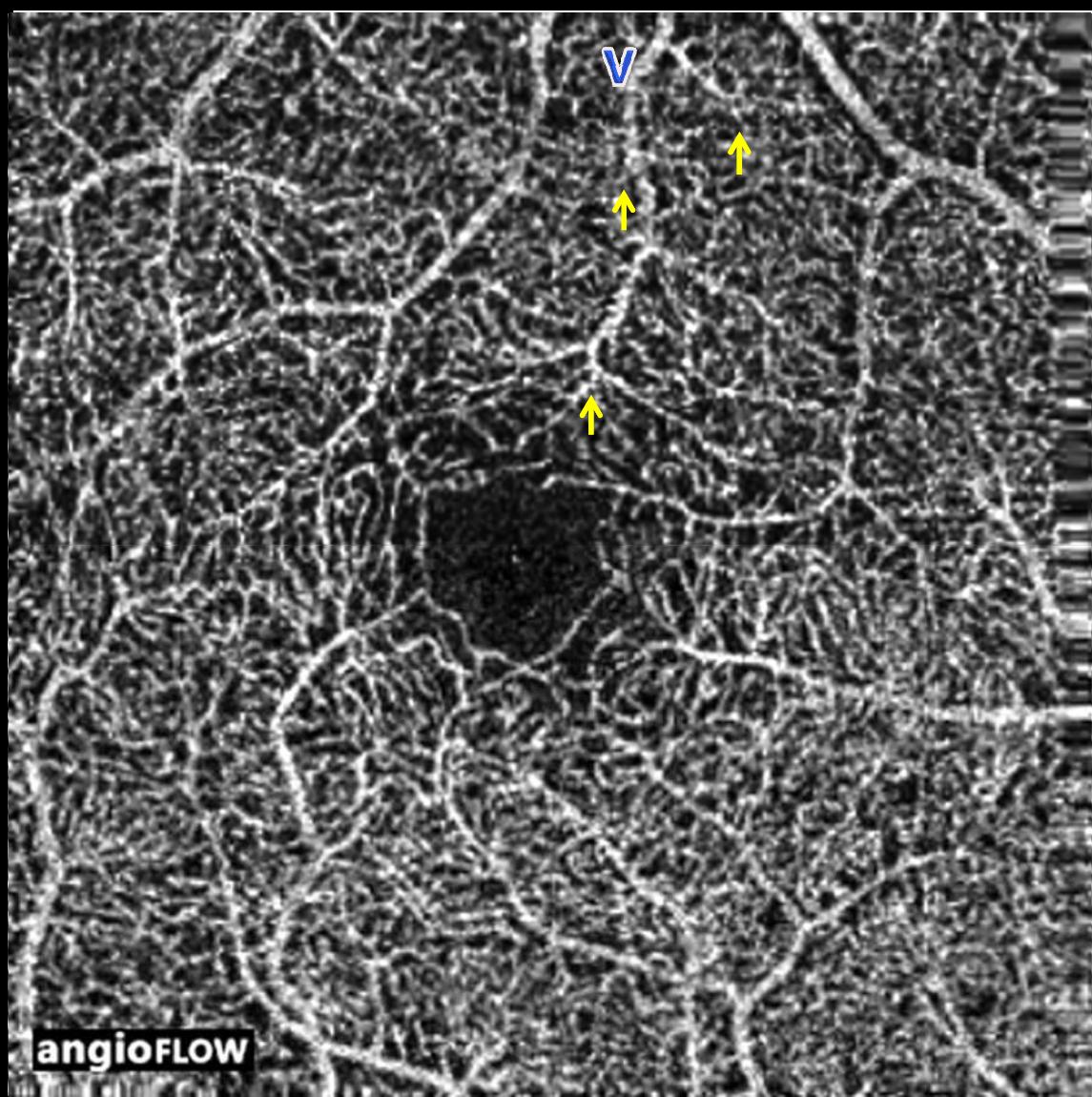
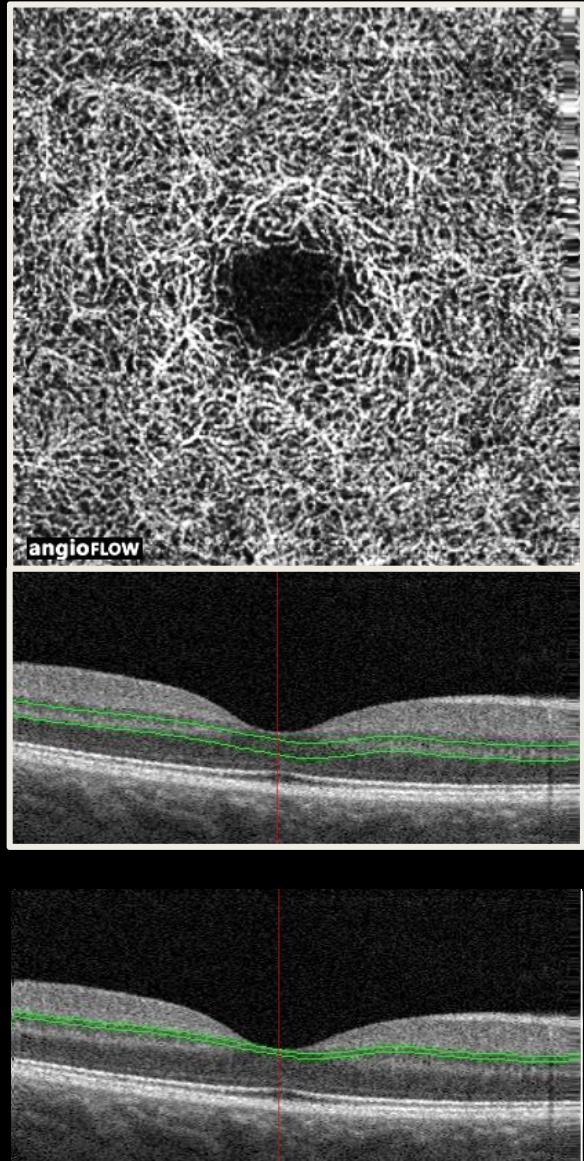


Genevois et al, 2004

The three outer layers are very similar across mammals;
the RPCs differs according to the number of RGCs and hence to the size of the eye

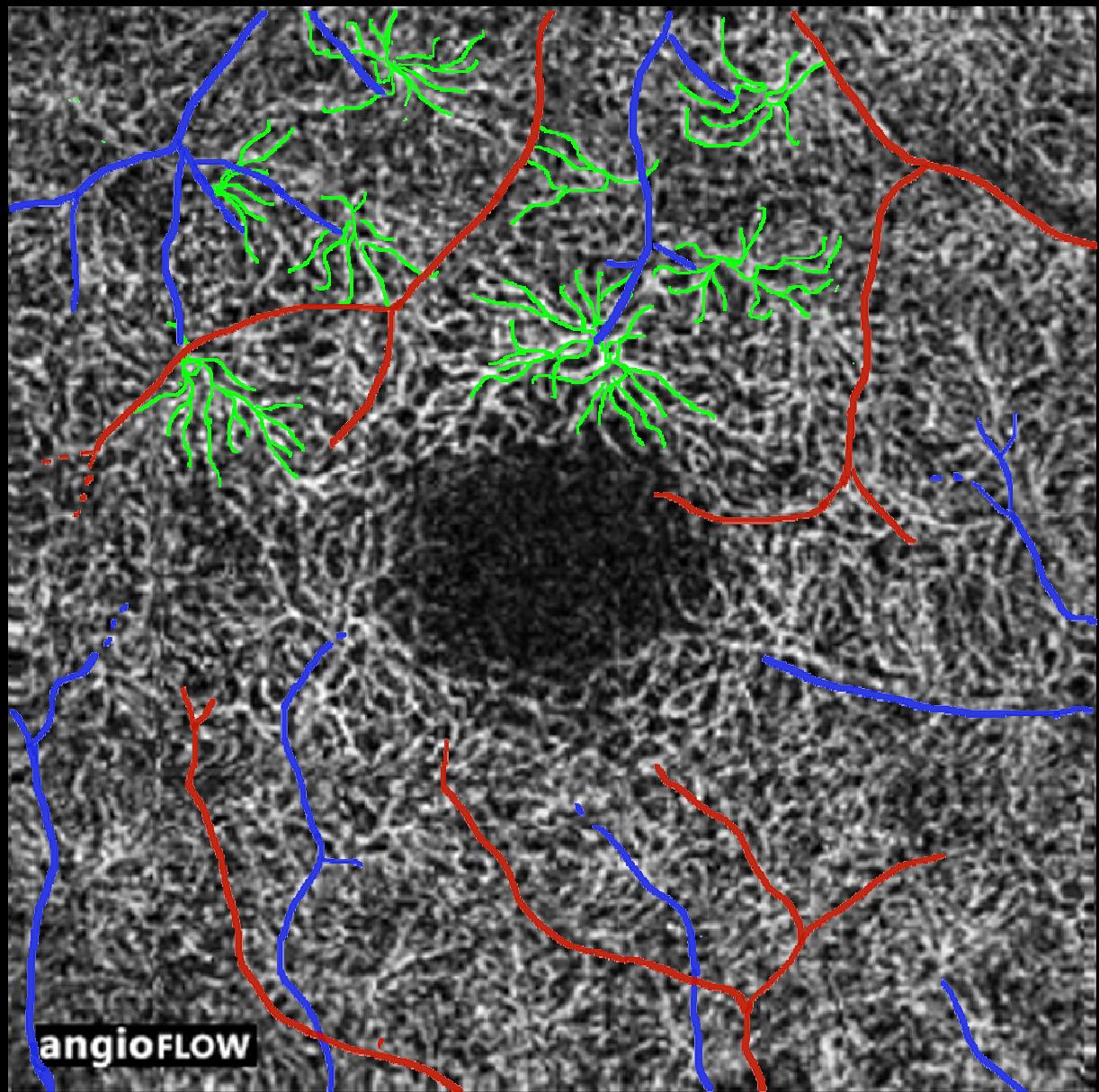
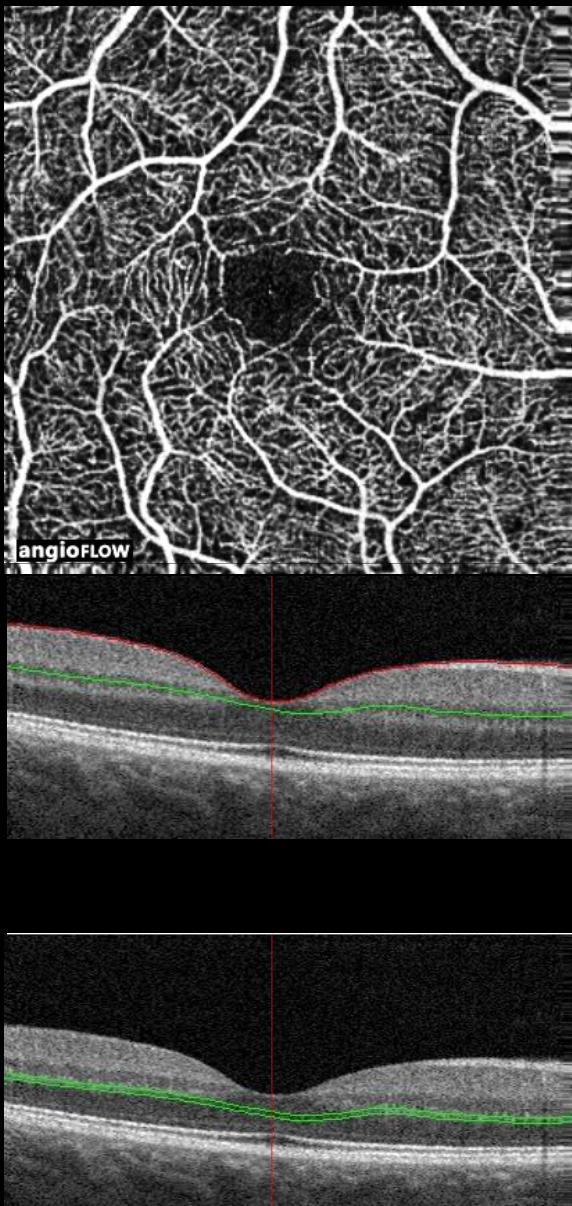


Pattern of the deep capillary plexus



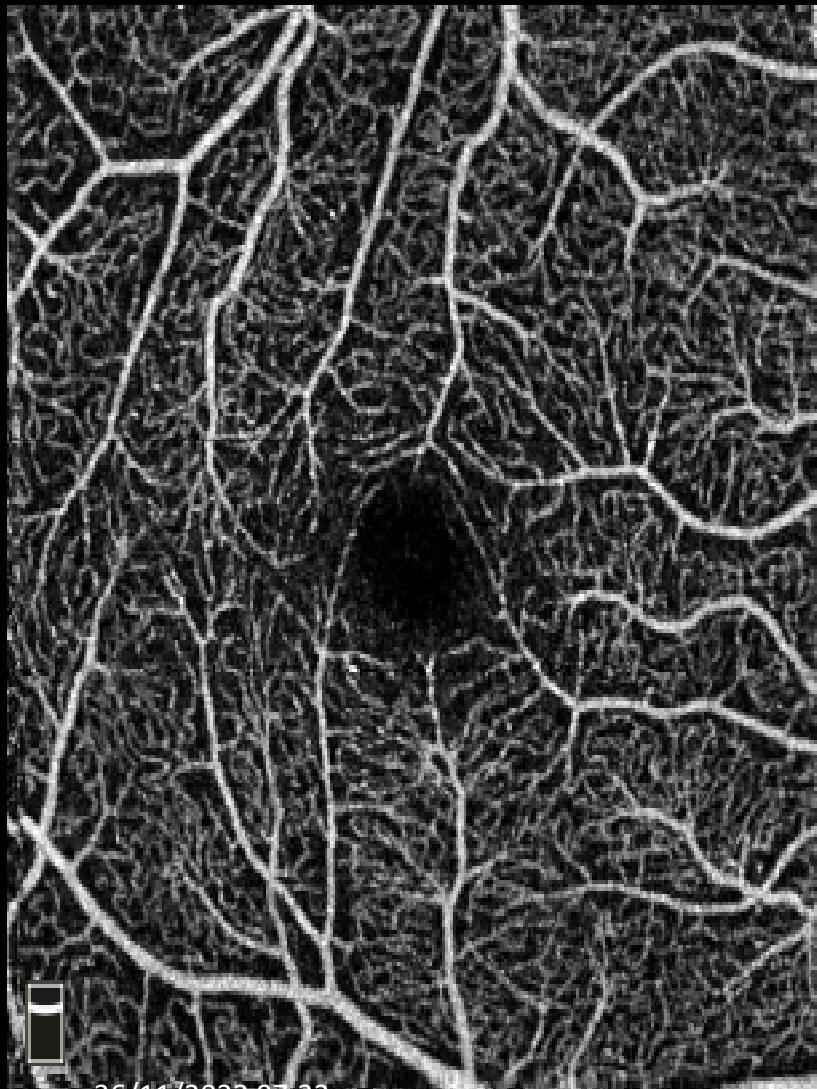
From deep to front

Vortex veineux dans la DVP



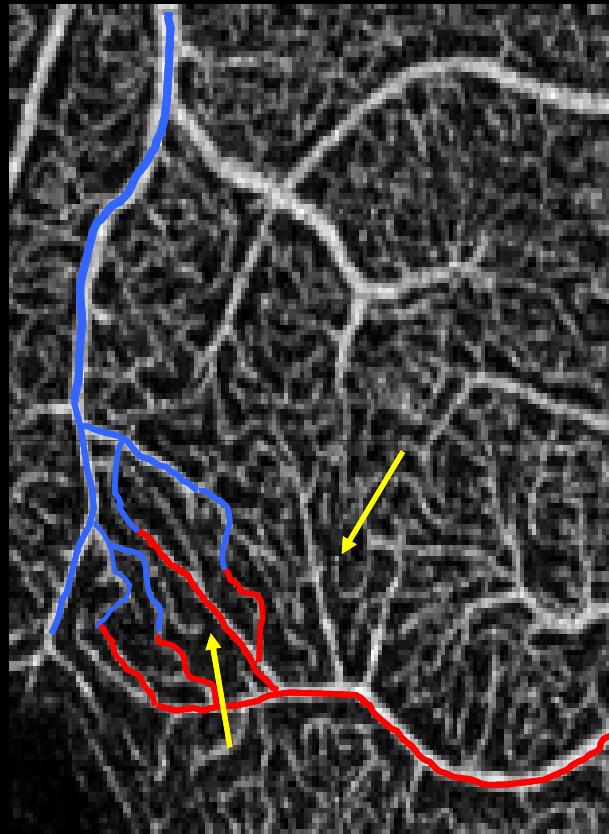
Superficial vessel plexus

30



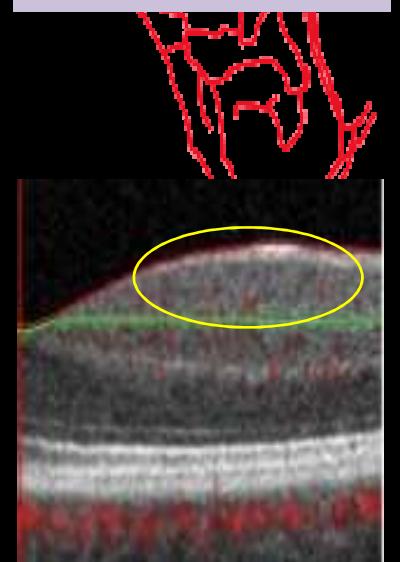
26/11/2022 07:33

Hôpital Lariboisière Ophtalmopôle de Paris



Retinal capillaries also feed the underlying plexuses

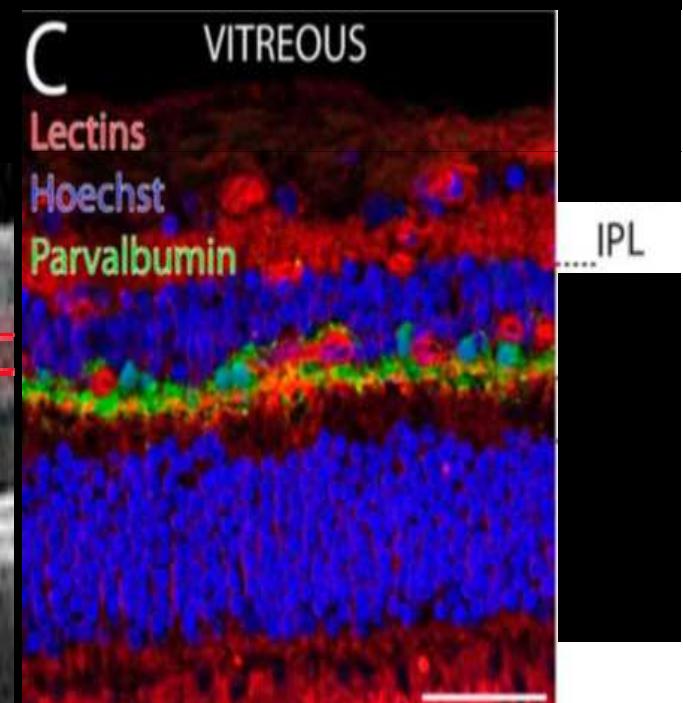
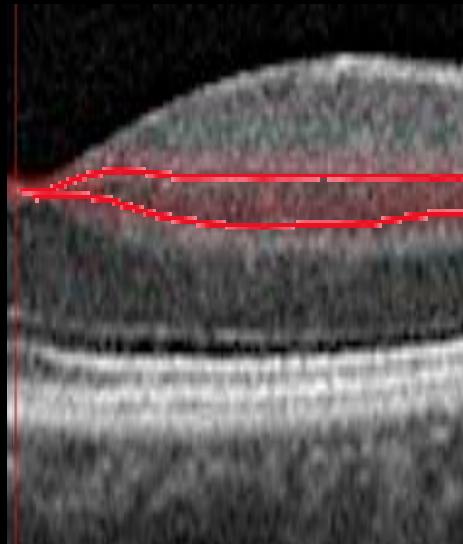
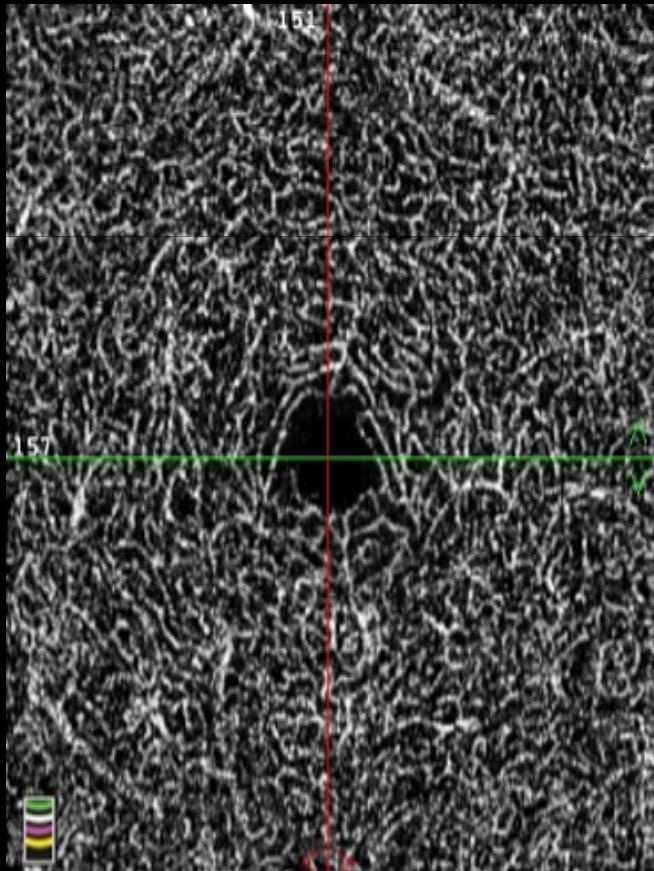
Although the capillaries of the SVP appear on OCTA as a single plane , they actually have a 3-D organization in the thick macular ganglion cell layer



Intermediate Capillary Plexus

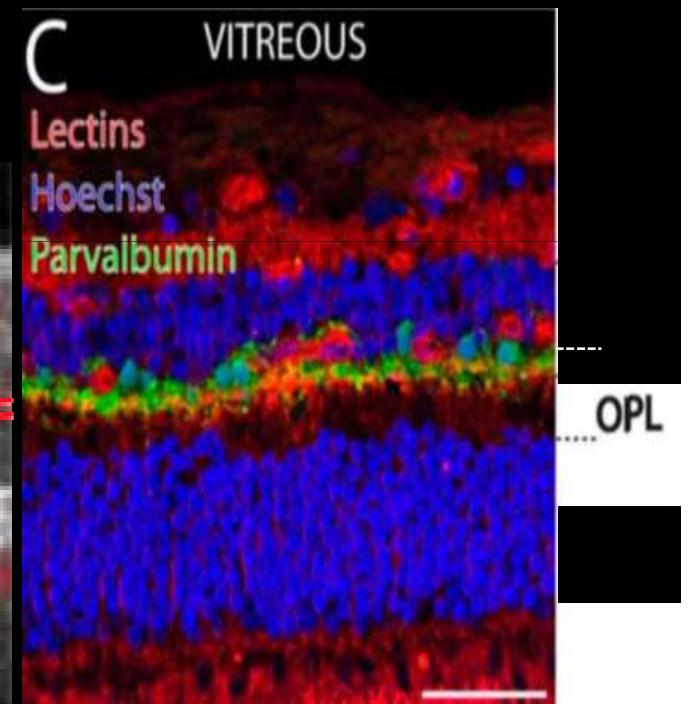
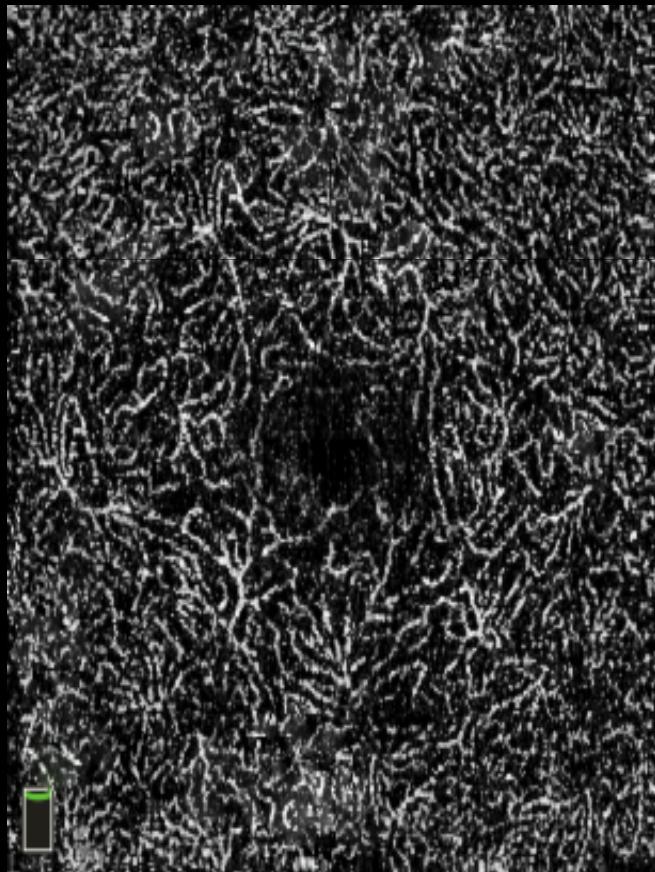
31

- is located in the outer part of the IPL

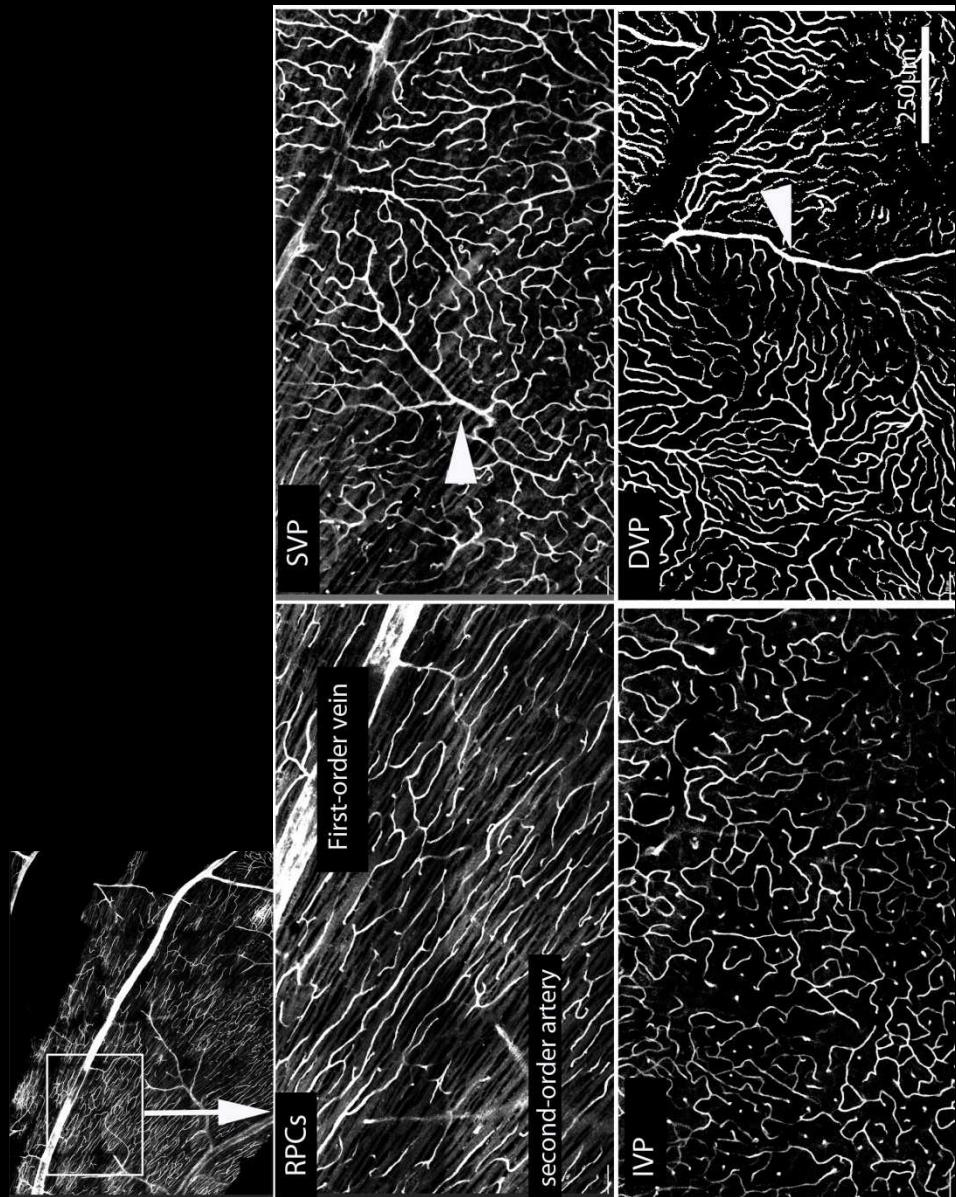


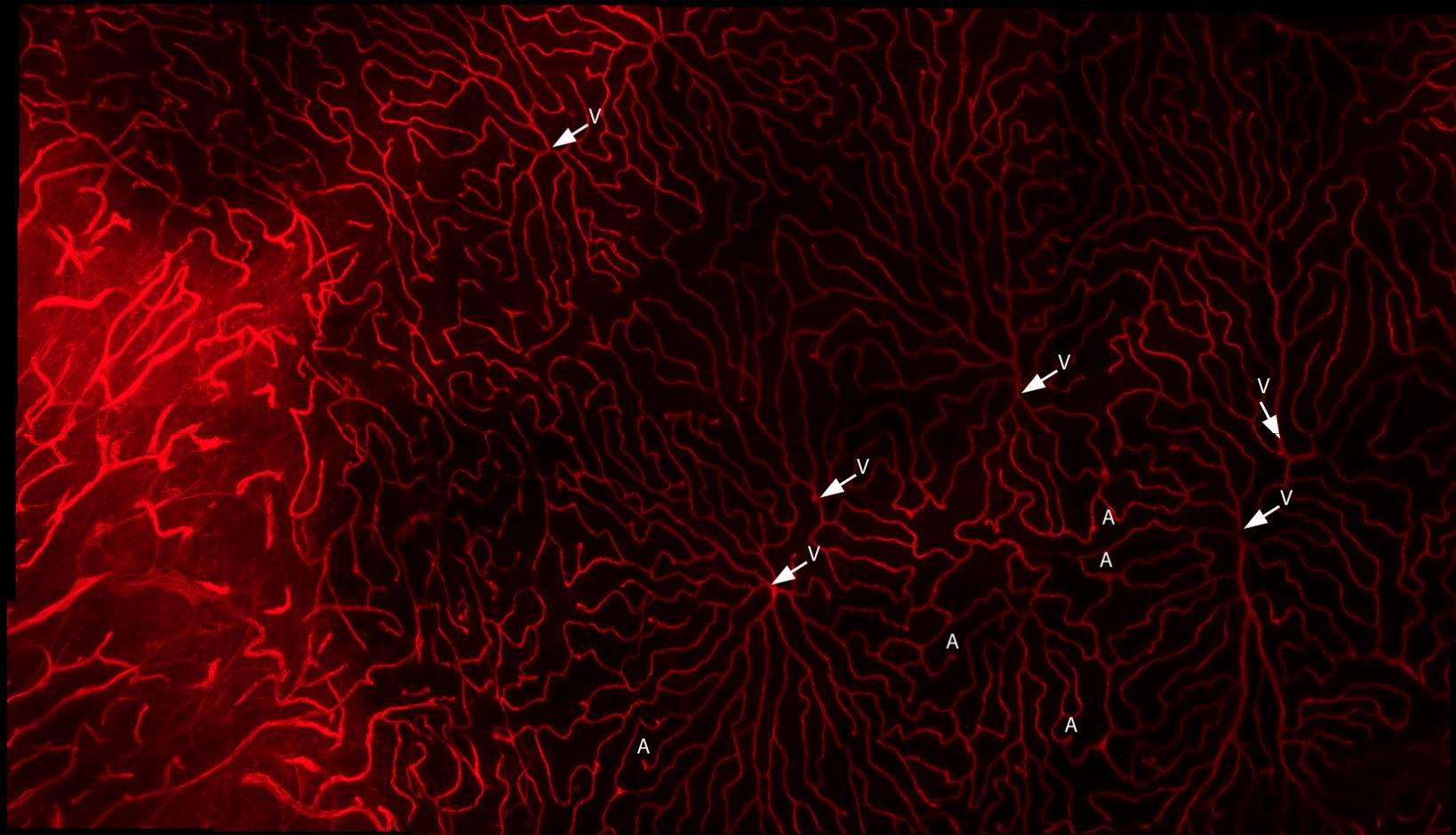
Deep Capillary Plexus

- DCP is the outer layer of the DCC
 - capillaries are located just above the Outer Plexiform Layer



- They are characterized by their organization converging to a central drainage venule

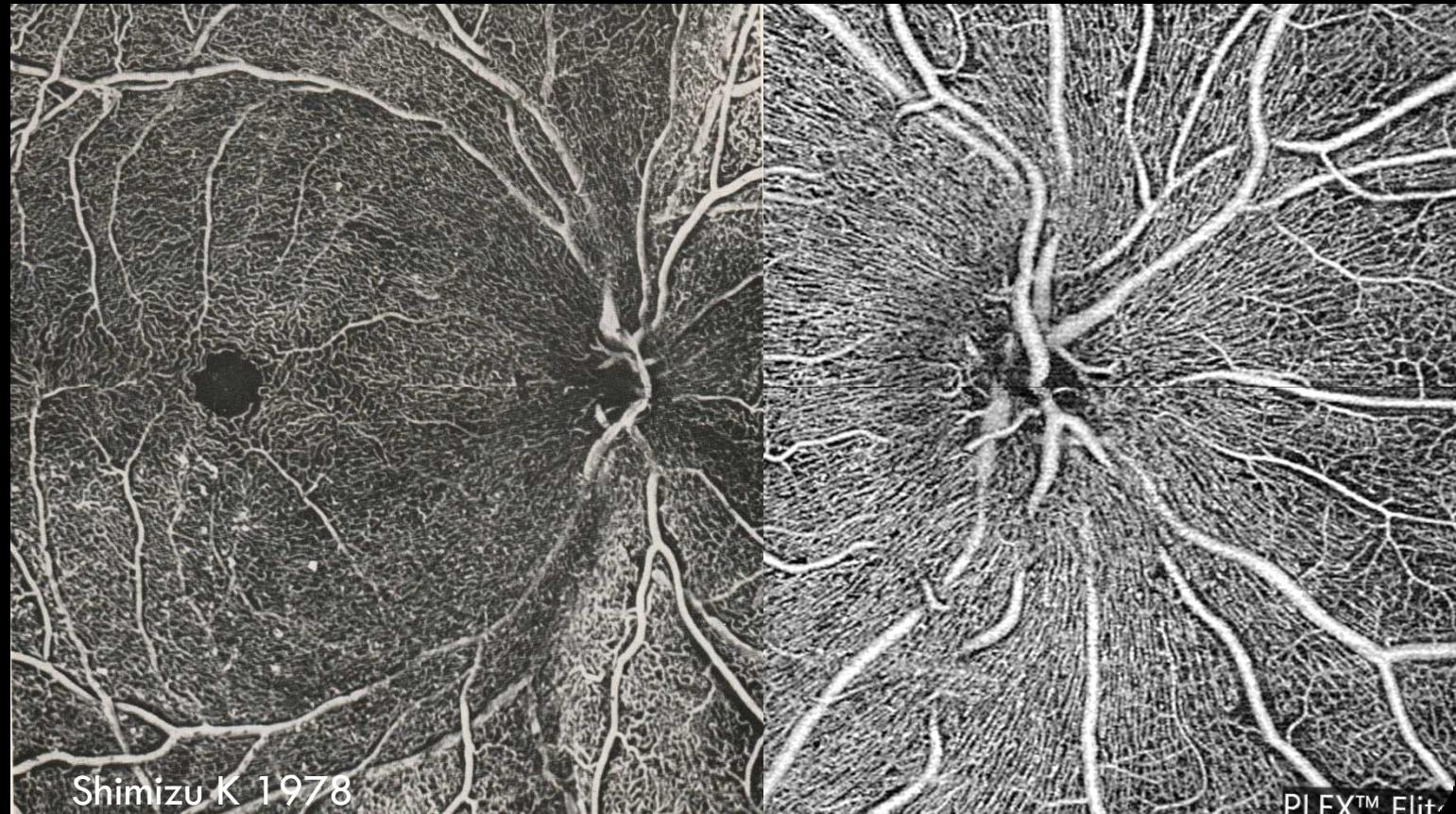




La DVP est anastomotique sur toute sa surface

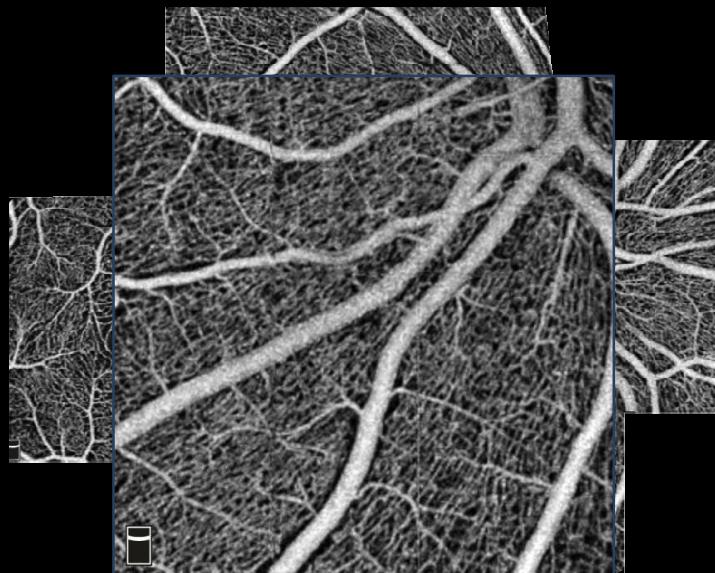
Capillaires radiaires péripapillaires

Une couche supplémentaire de capillaires pour les fibres optiques



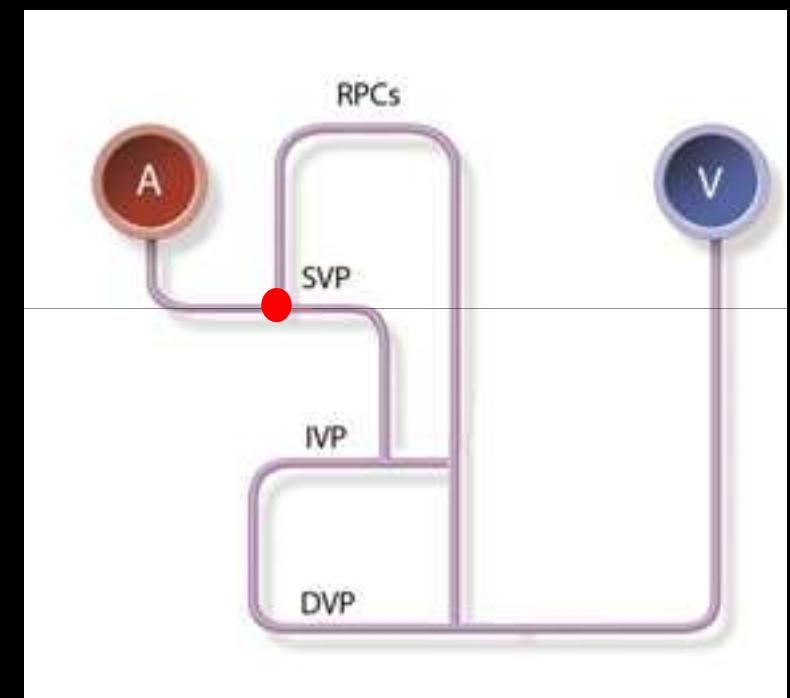
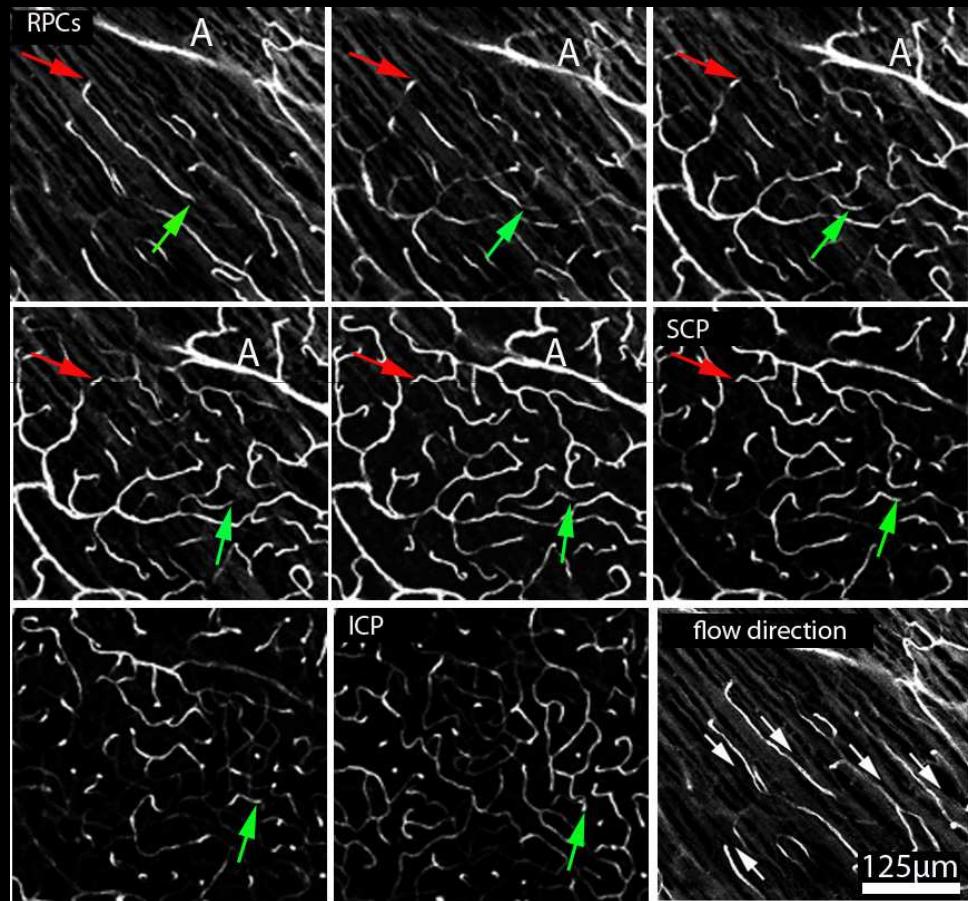
Large mammalian eyes: Radial peripapillary capillaries

- The NFL elicits its own capillary network, which varies in thickness in parallel to the amount of NFLs
- Small eyes have a very limited amount of NFL and hence a small amount of radial peripapillary capillaries
- In large eyes, the thickness of the retina increases mostly because of the thickness of the NFL, and hence the RPCs contingent increases with the size of the eye

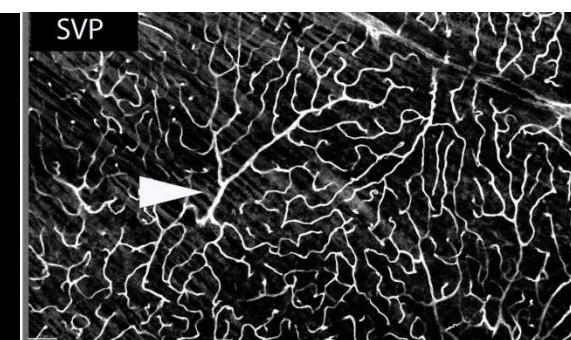
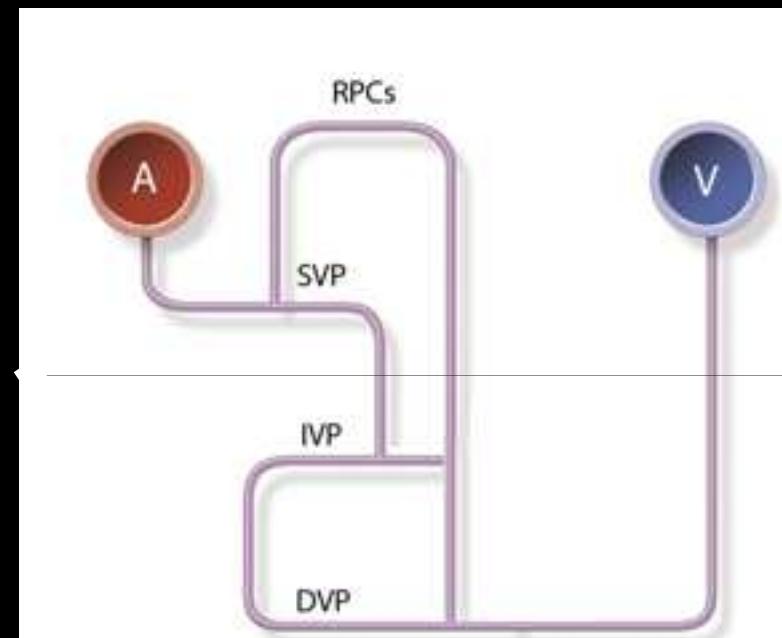
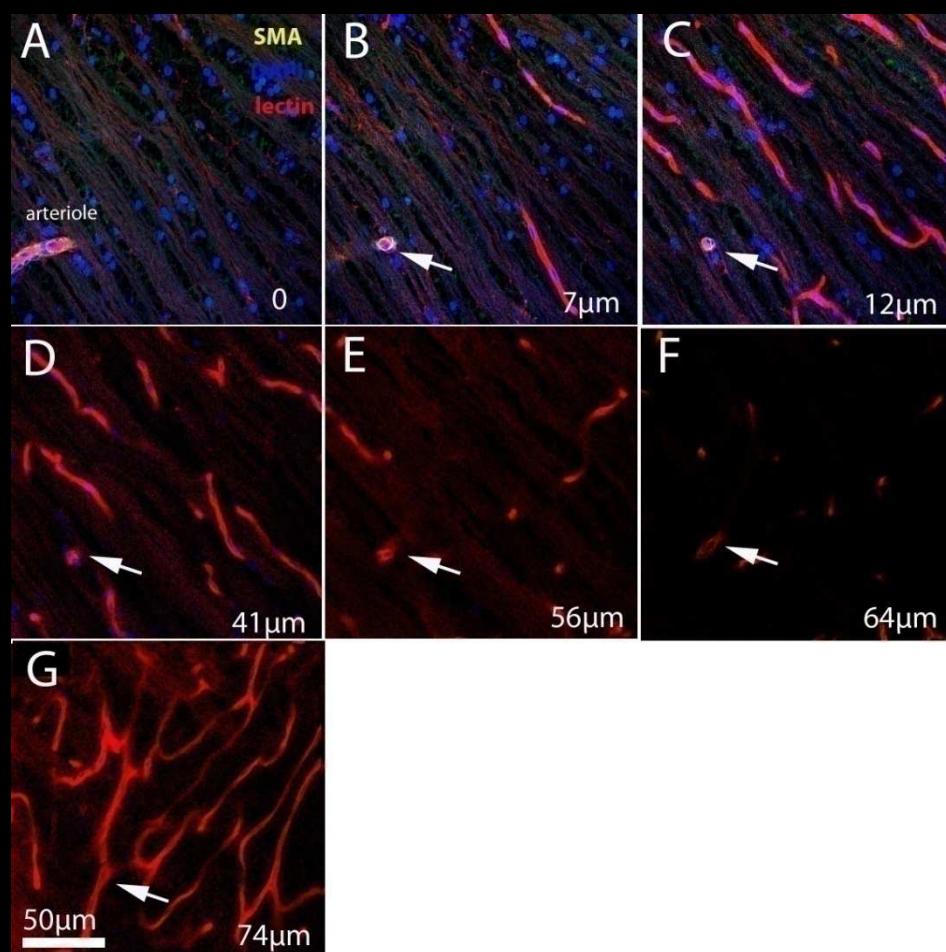


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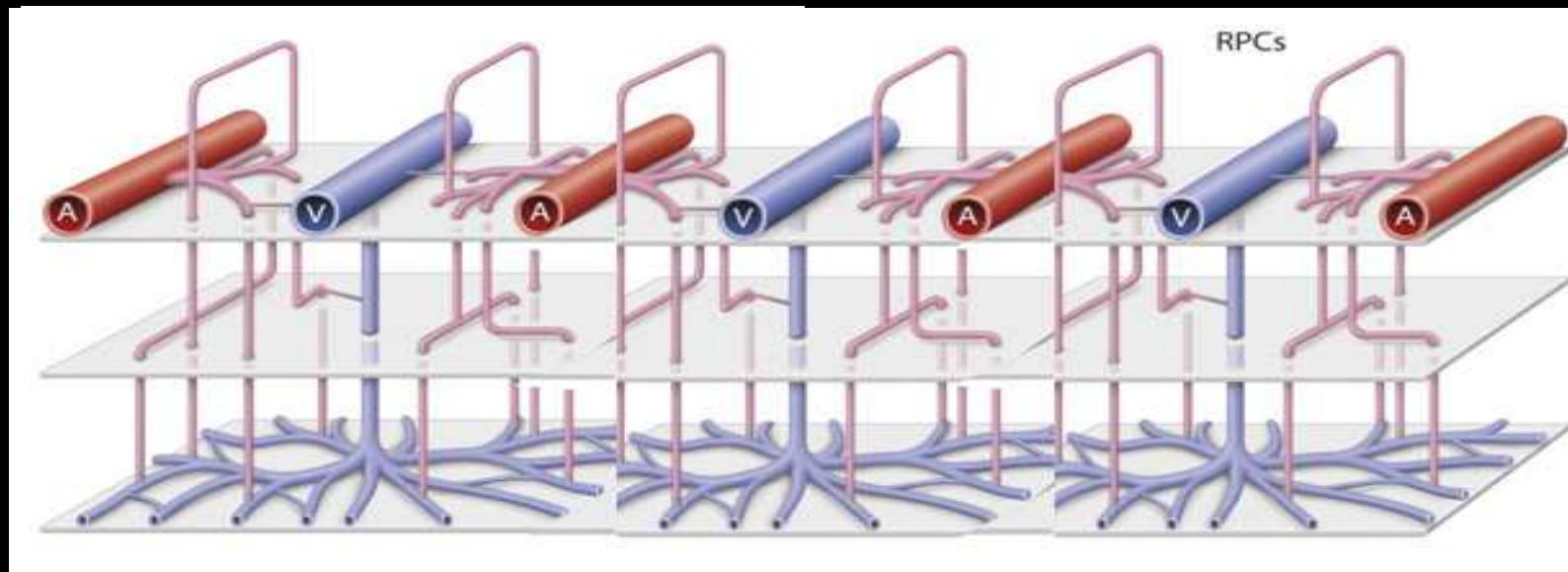
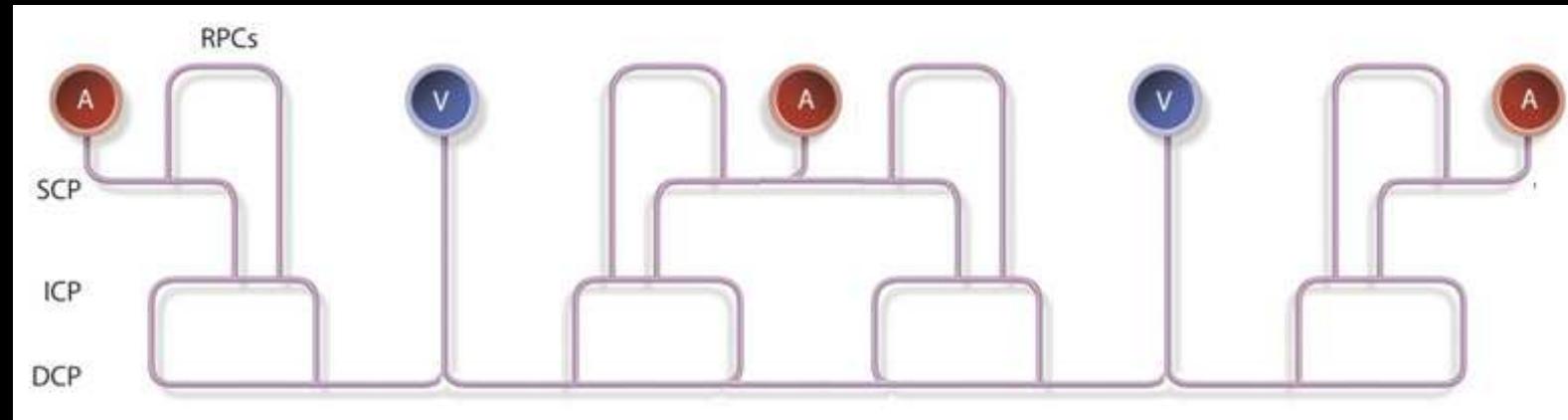
RPCs have asymmetric connections: one foot in the SVP, another one deeper in the IVP/DVP



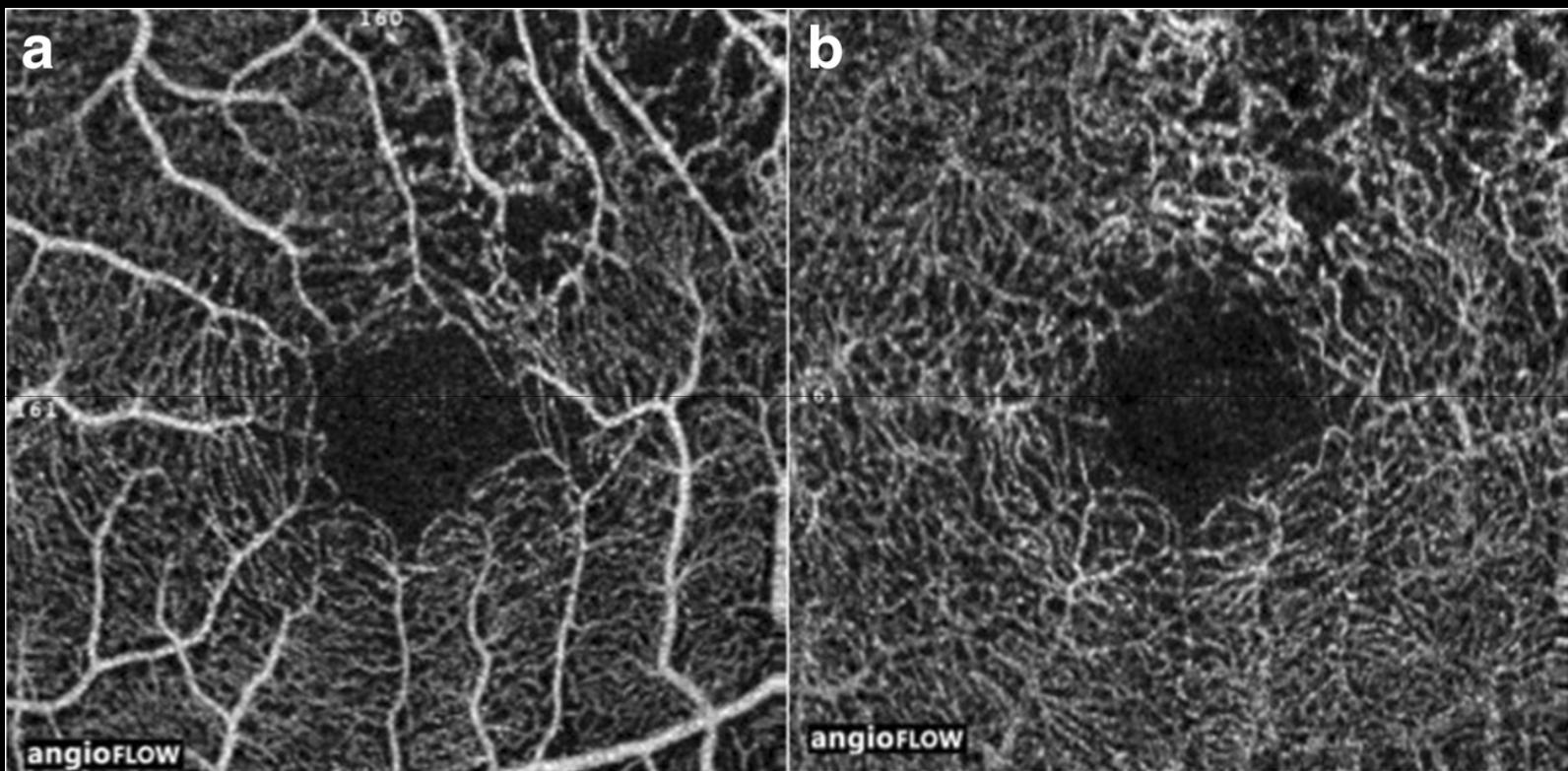
Arterioles only connect to the SVP; therefore the SVP is a crossroads for arteriolar flow, dichotomizing blood flow to the RPCs and to the outermost layers



Models of the capillary circulation in the holangiotic retina

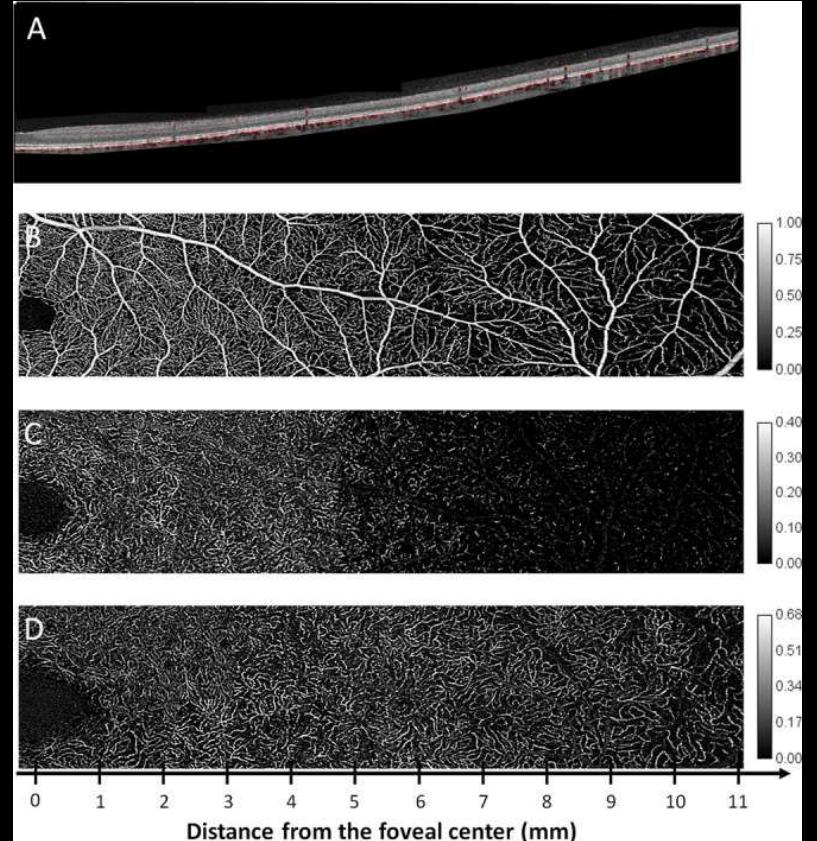
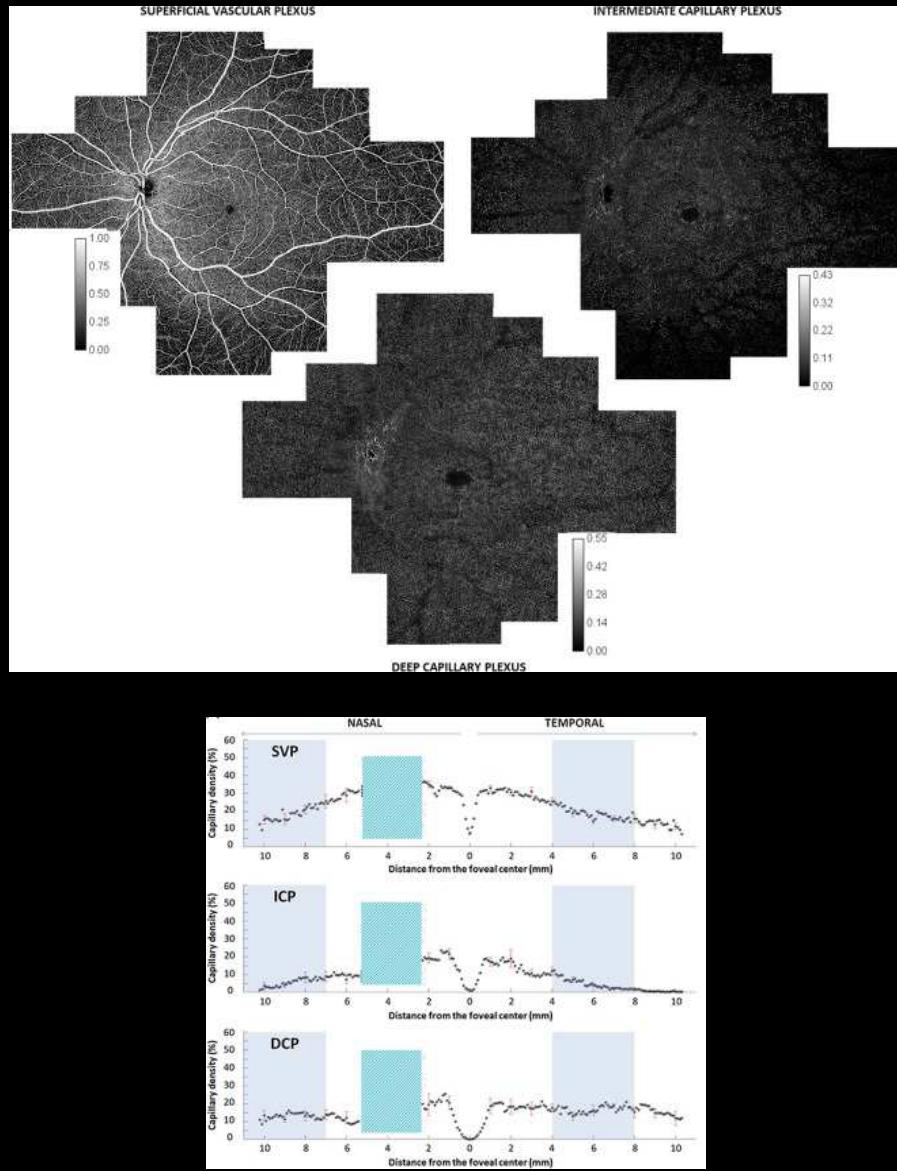


Les collatérales se développent surtout dans le réseau profond



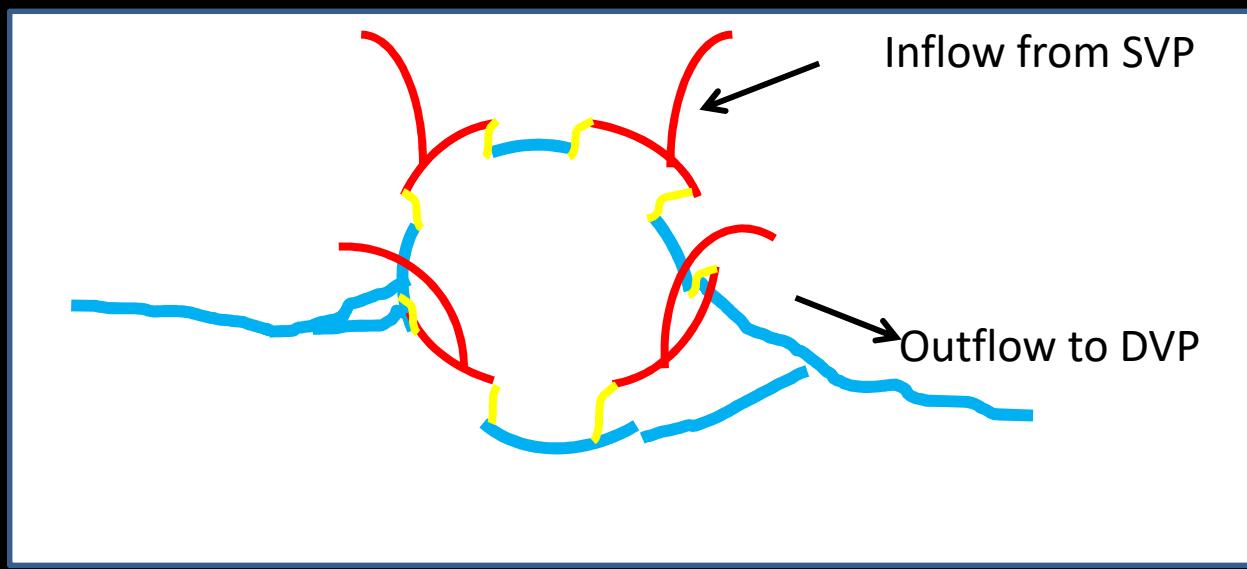
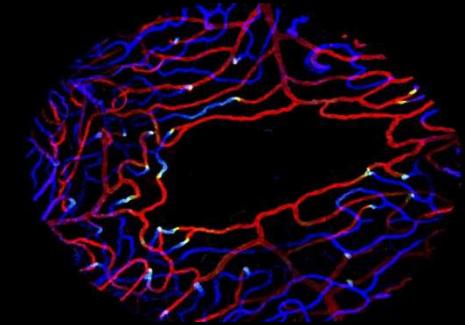
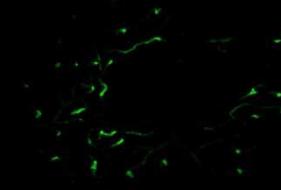
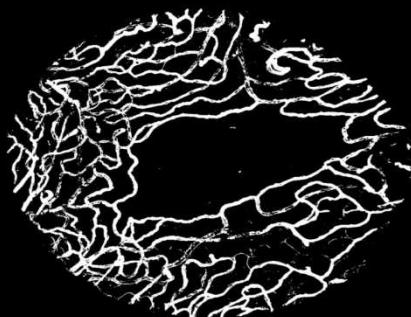
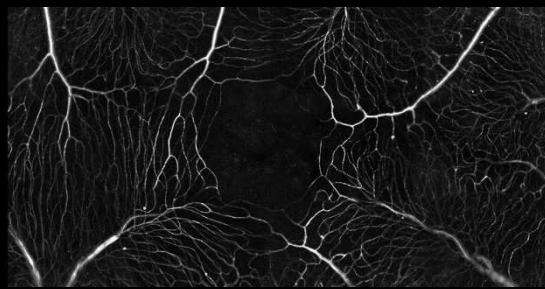
- Wang et coll. Gaefe 2018; Freund et coll, JAMA ophth 2018

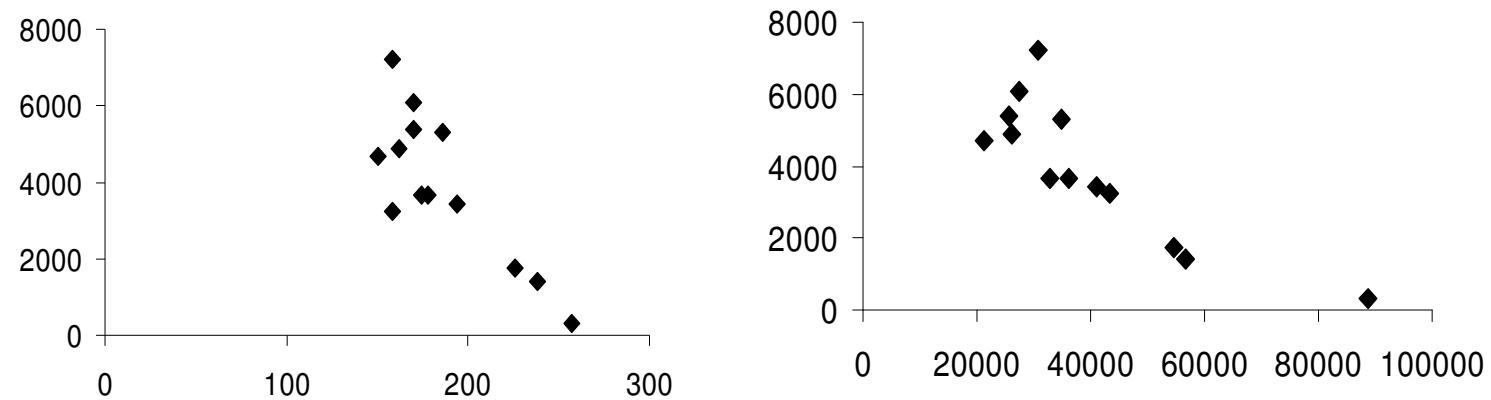
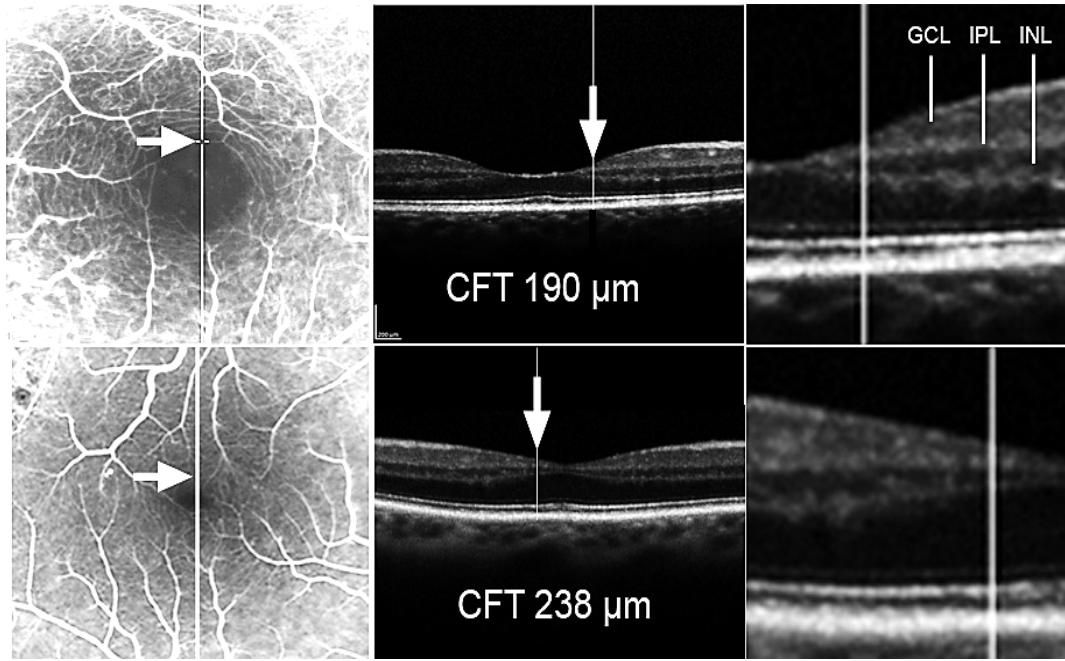
Capillary patterns varies with eccentricity

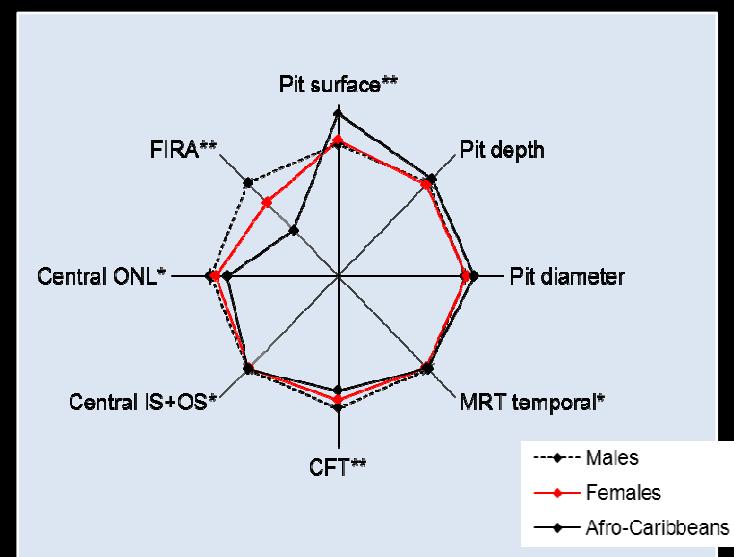
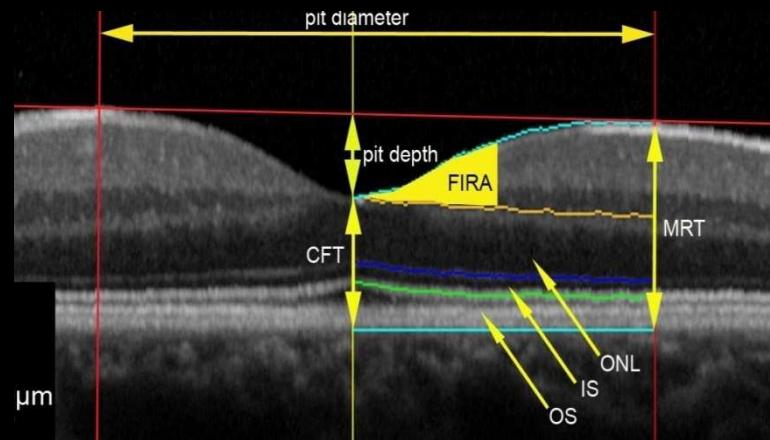
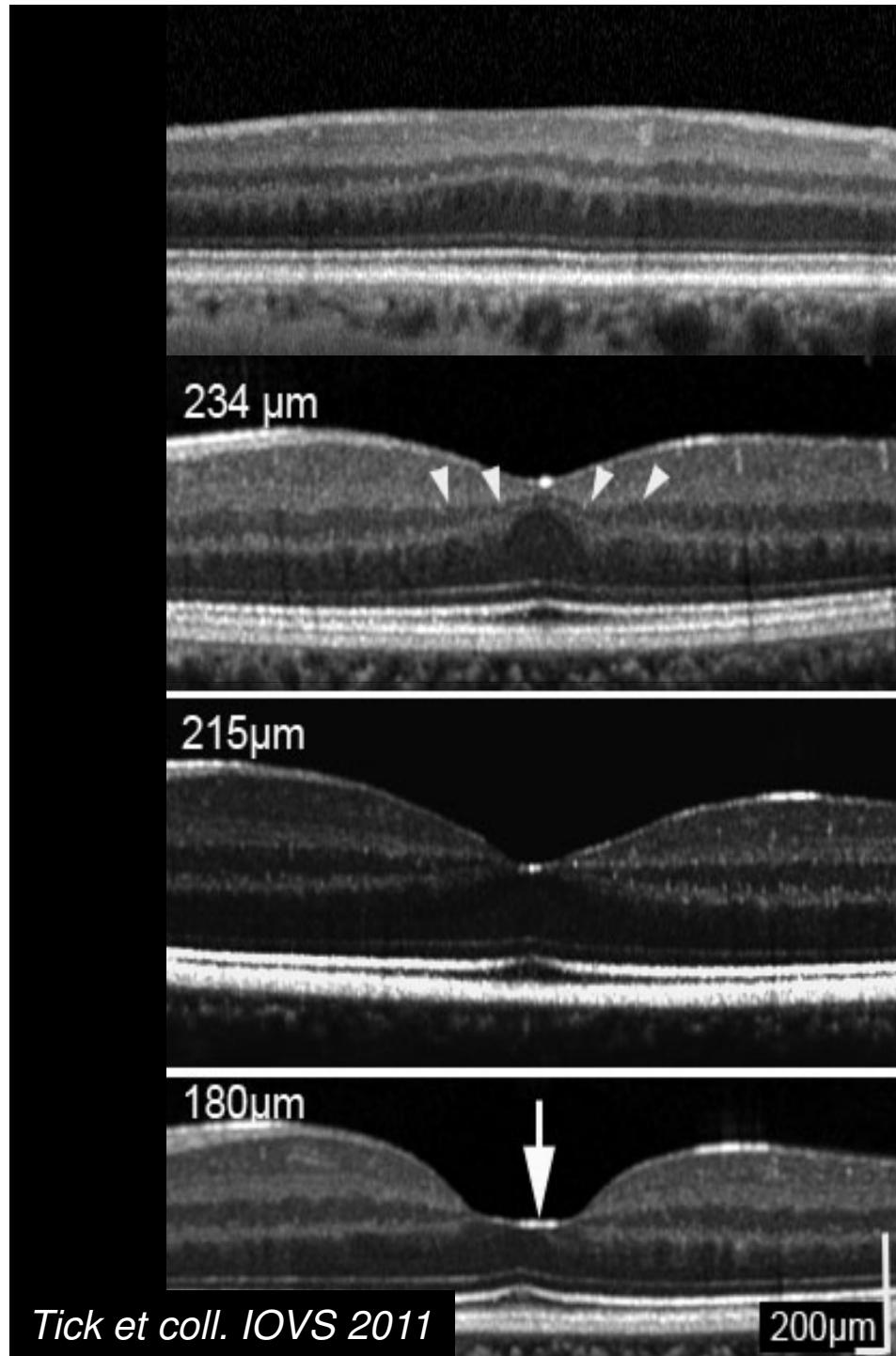


Lavia et coll 2019

Probable perfusion de la surface vers la profondeur



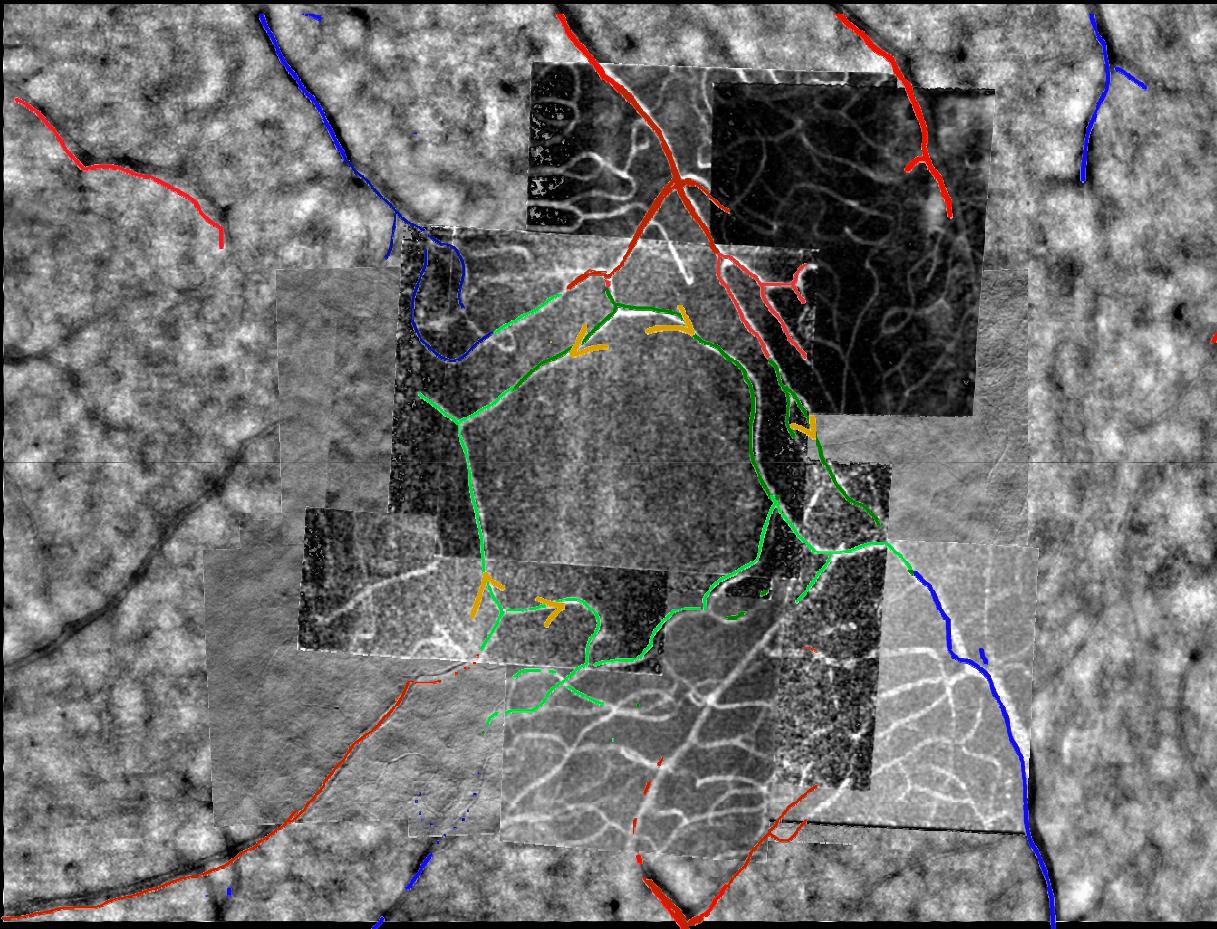




> Ophthalmology. 1999 Jul;106(7):1409-13. doi: 10.1016/S0161-6420(99)00732-0.

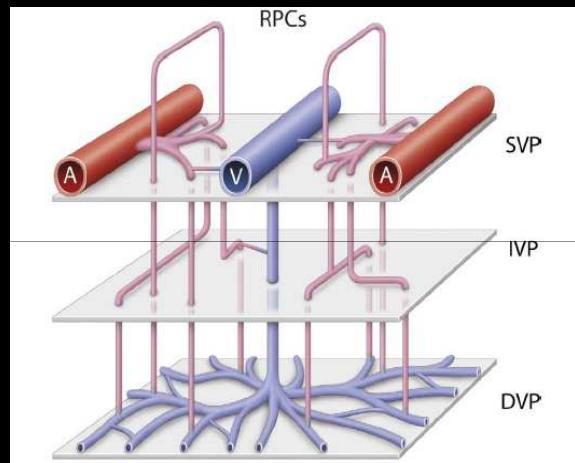
A small foveal avascular zone may be an historic mark of prematurity

H A Mintz-Hittner[†], D M Knight-Nanan, D R Satriano, F L Kretzer



Thèse S Bonnin

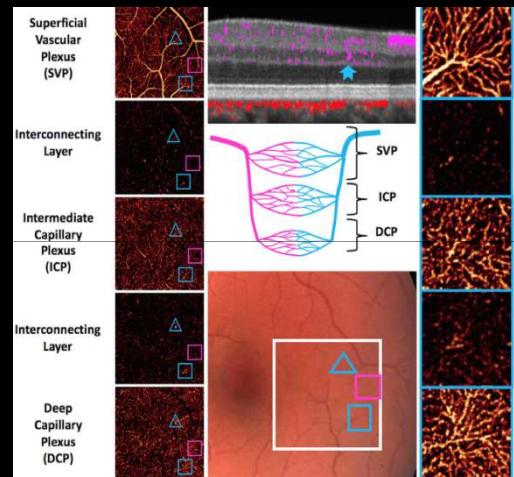
3D schematization of the retinal capillaries



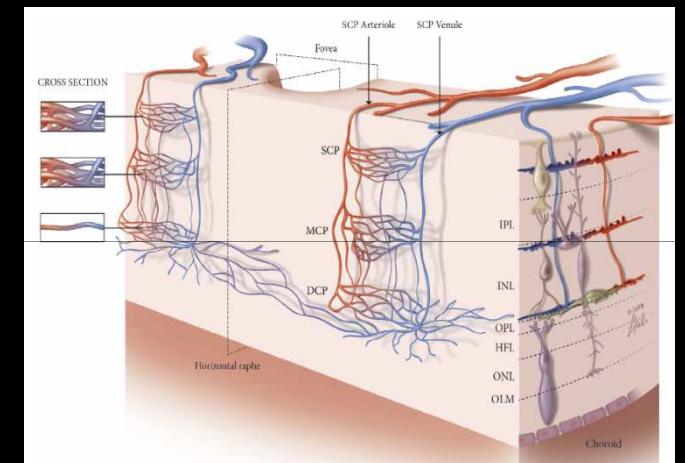
The 3D Retinal Capillary Circulation in Pigs Reveals a Predominant Serial Organization

Stéphane Fouquet,¹ Ophélie Vacca,¹ Florian Sennlaub,¹ and Michel Paques^{1,2}

Invest Ophthalmol & Vis Sci.
2017;58(13):5754-5763.



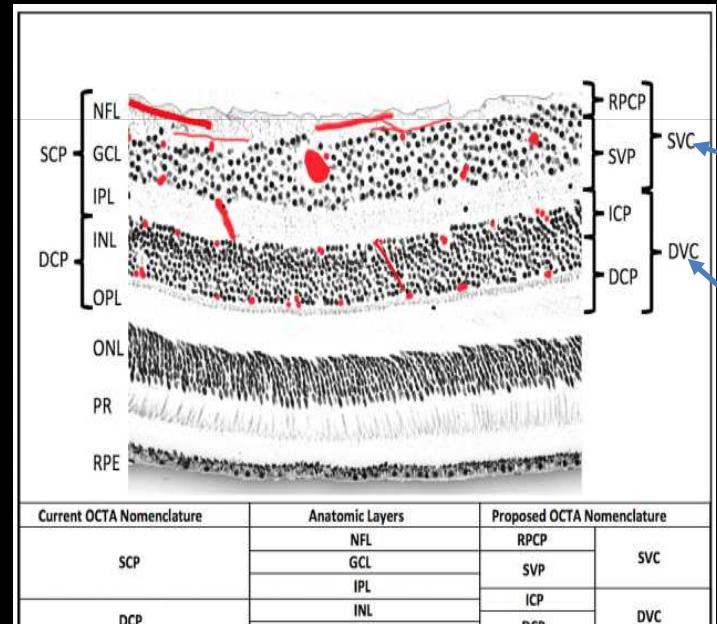
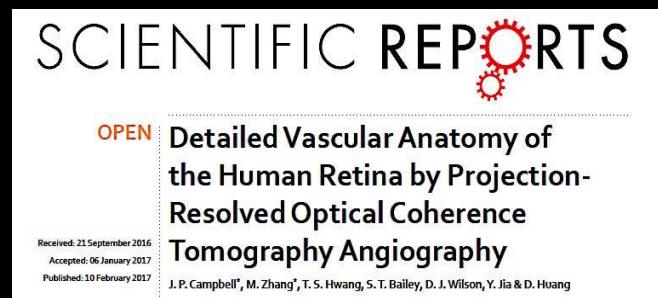
Campbell JP, Zhang M, Hwang TS, et al. Detailed Vascular Anatomy of the Human Retina by Projection-Resolved Optical Coherence Tomography Angiography. *Sci Rep.* 2017;7:42201.



Nesper PL, Fawzi AA. Human Parafoveal Capillary Vascular Anatomy and Connectivity Revealed by Optical Coherence Tomography Angiography. *Investigative Ophthalmology & Visual Science.* 2018;59(10):3858-3867.

Nomenclature

47



- To name the retinal capillary layers we used the terminology proposed by Campbell et al

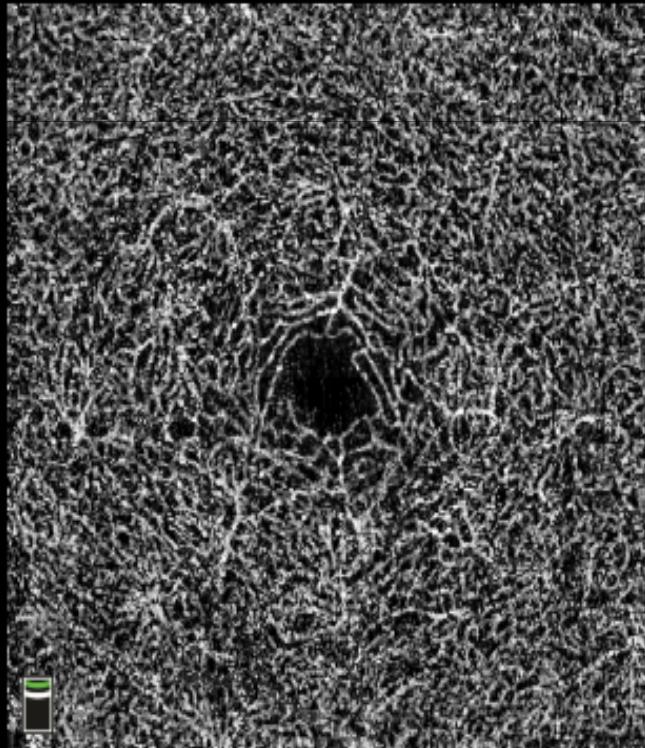
SUPERFICIAL VASCULAR COMPLEX =
Radial Peripapillary Capillary plexus
+ Superficial Vascular Plexus

DEEP VASCULAR COMPLEX =
Intermediate Capillary plexus
+ Deep Vascular Plexus

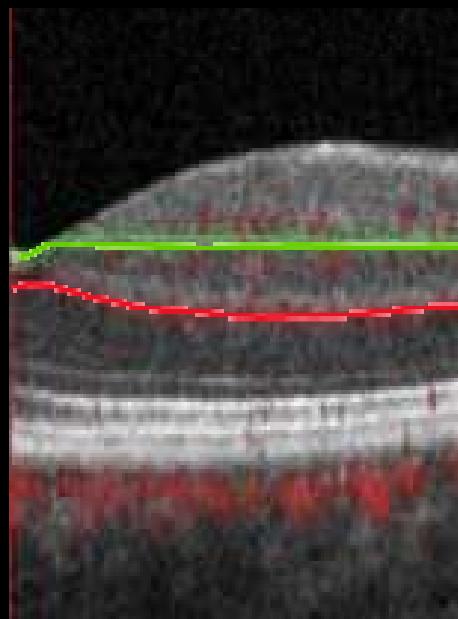
Deep Vascular Complex (DVC) ICP+DCP

48

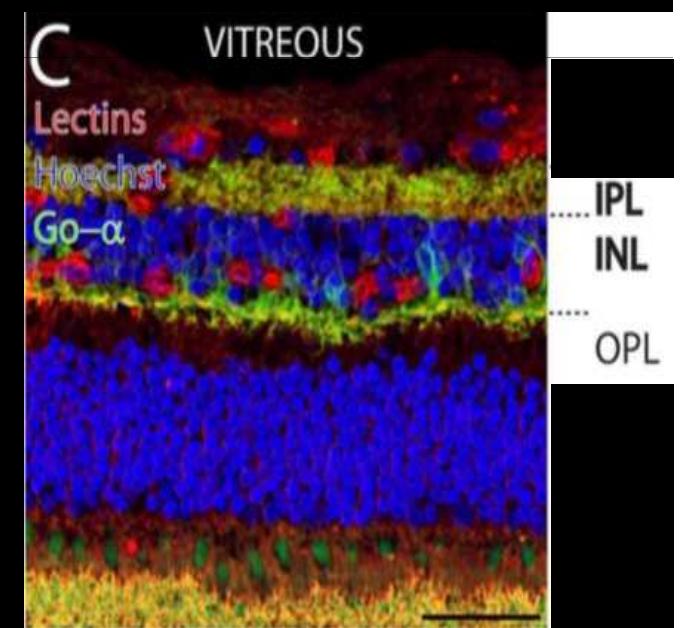
- Comprises two layers of capillaries which surround the INL
 - capillaries are located in the inner and outer plexiform layers



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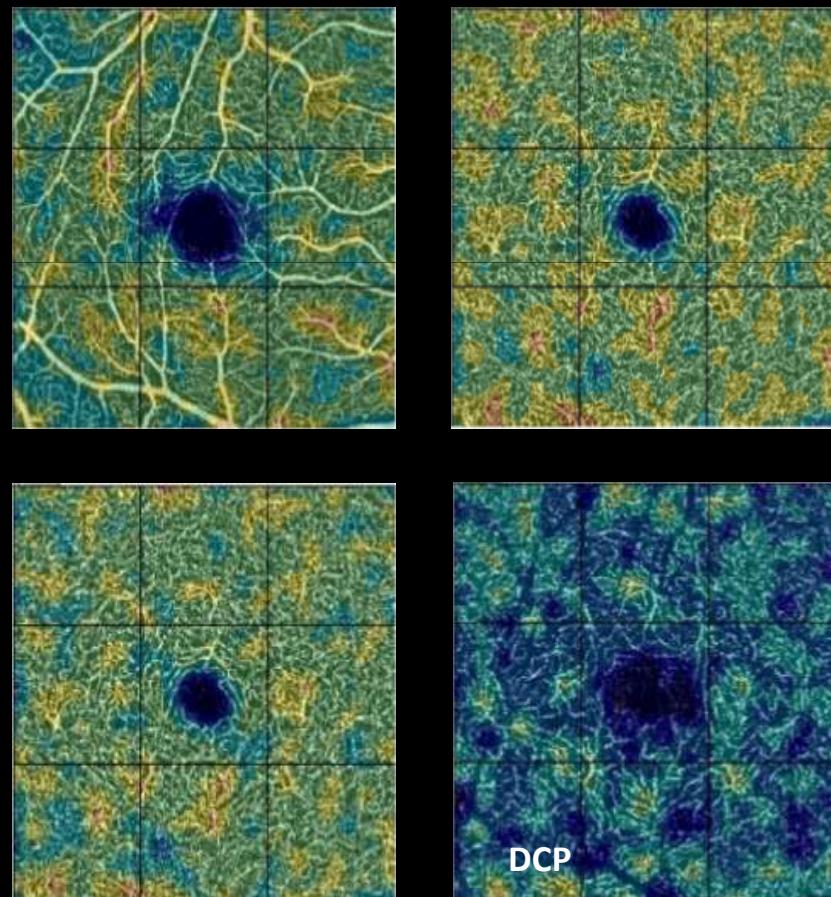
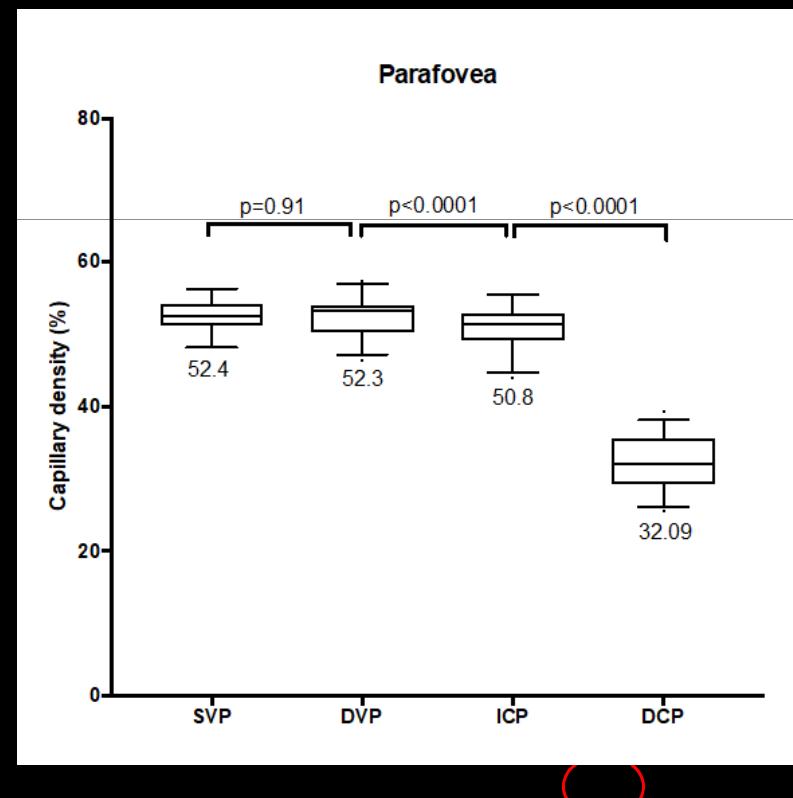
Hôpital Lariboisière Ophtalmopôle de Paris



Tan PEZ, et al. *Invest Ophthalmol Vis Sci*. 2012;53(9):5728-5736.

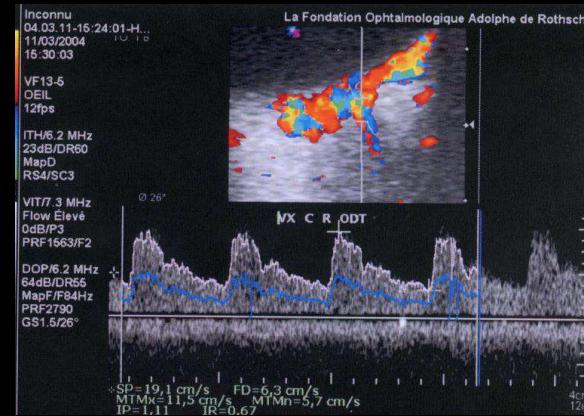
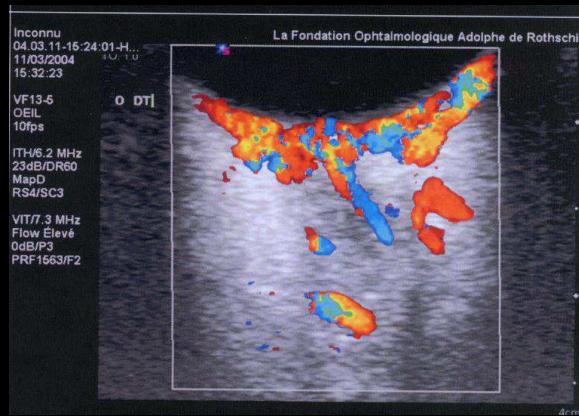
Capillary density of macular plexuses

- In normal eyes, capillary density is the lowest in the Deep Capillary Plexus, the outer part of the Deep Vascular Complex



Pressions et débit sanguin rétinien & autorégulation

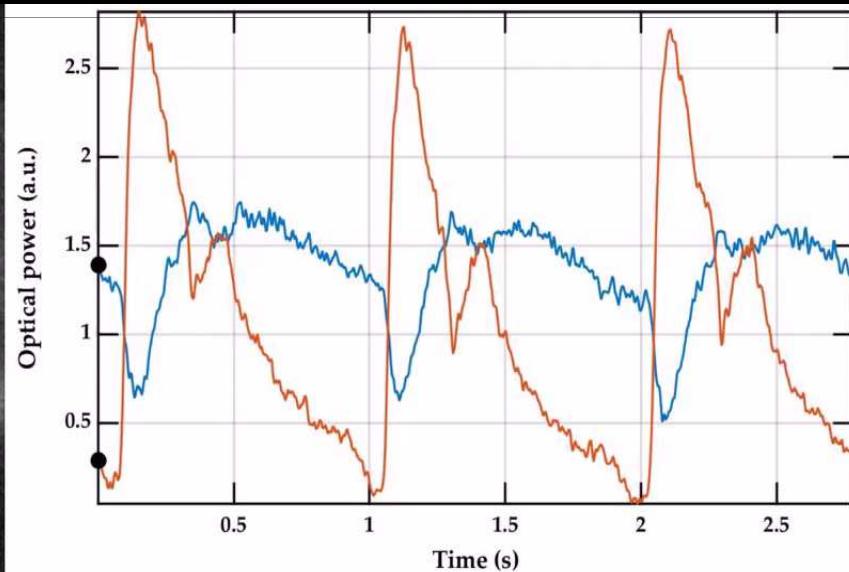
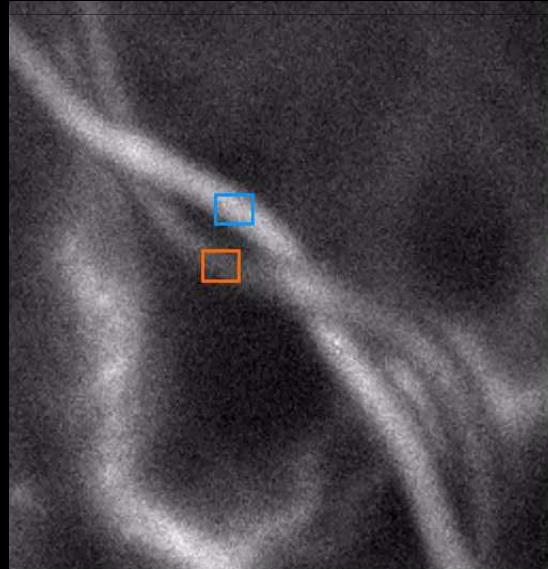
Echo doppler



Artères 8 à 15 cm/s
Veines 3 à 5 cm/s

Olivier Bergès (FOR)

Laser doppler



Puyo et al Biomed Optics Express 2018

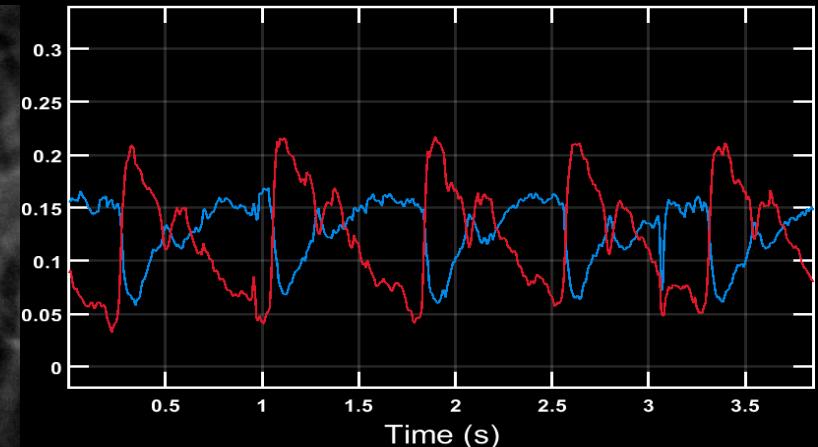
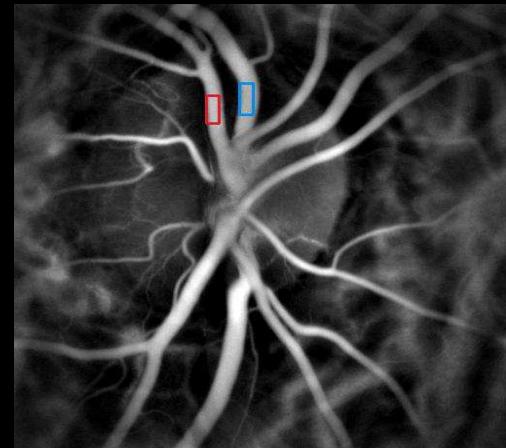
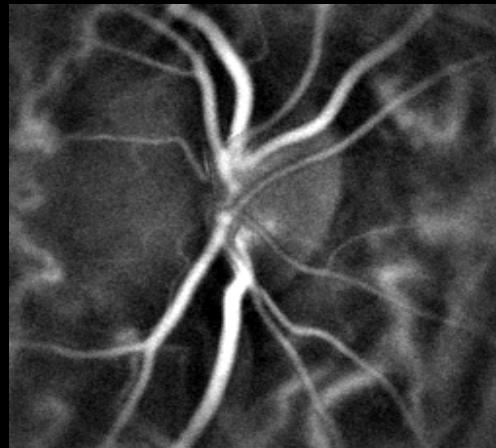
Laser Doppler holographique

V4

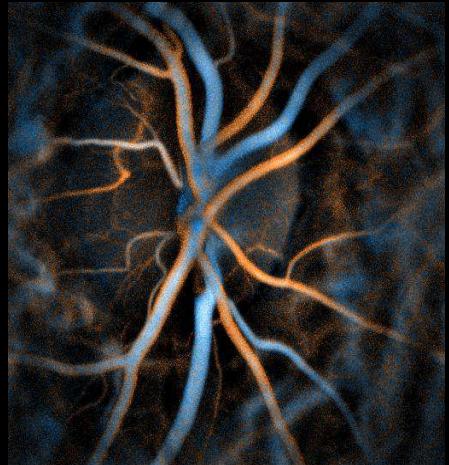
Power Doppler
movie (x0.8)

Power Doppler, 2-37 kHz

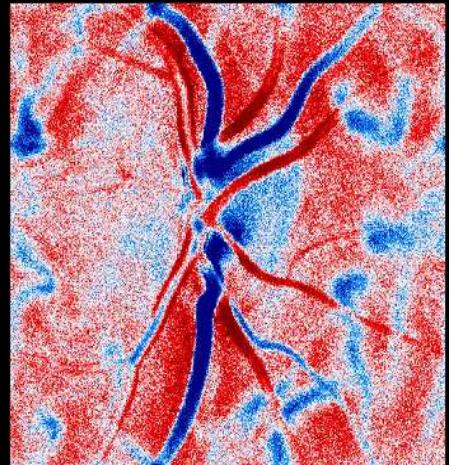
Power Doppler variations



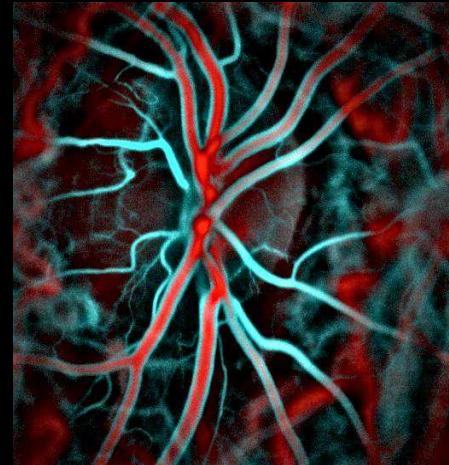
Systole / Diastole



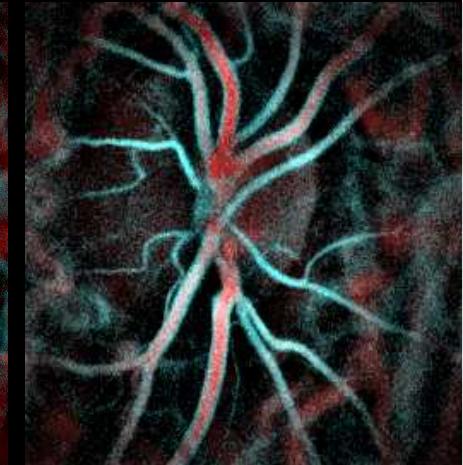
Resistivity map



Low flow / high flow



Composite movie

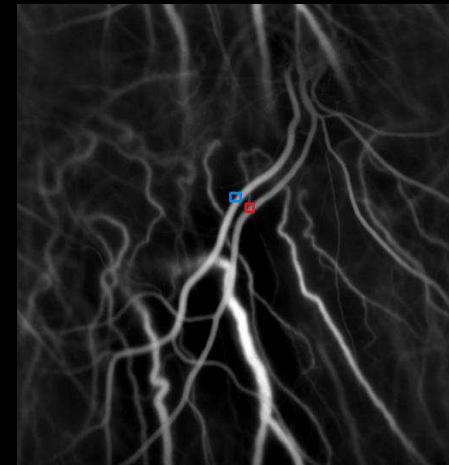


Laser Doppler holographique
Power Doppler
movie (x0.8)

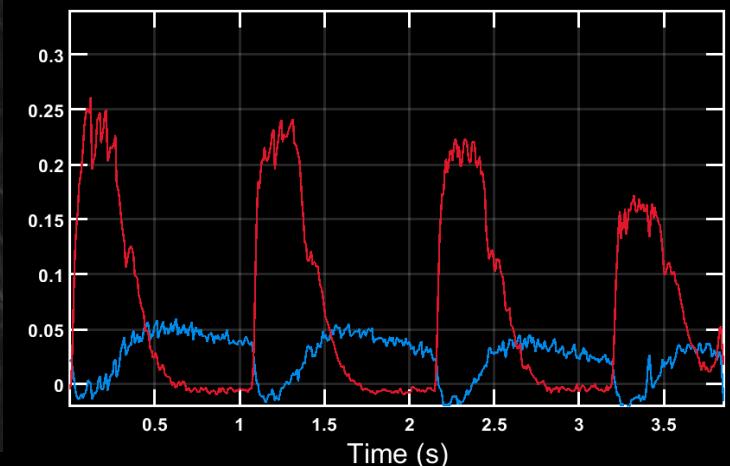
- IR = 0.89
- IP = 0.76
- IR = 0.46
- IP = 0.73



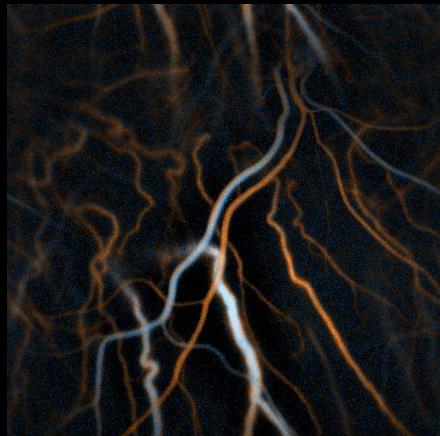
Power Doppler, 2-37 kHz



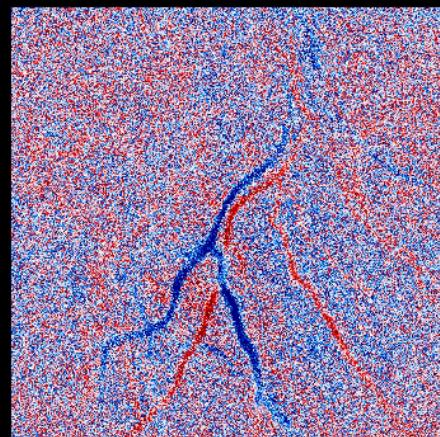
Power Doppler variations



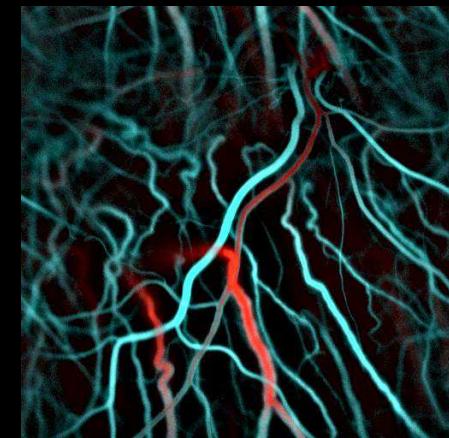
Systole / Diastole



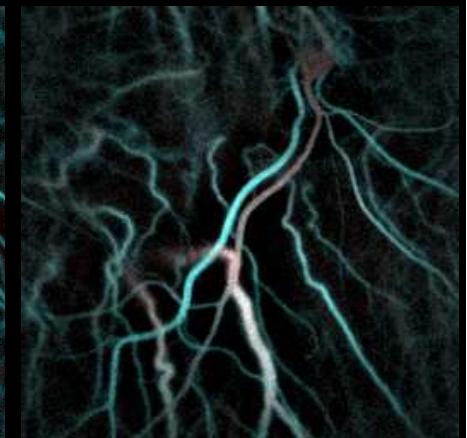
Resistivity map



Low flow / high flow



Composite movie

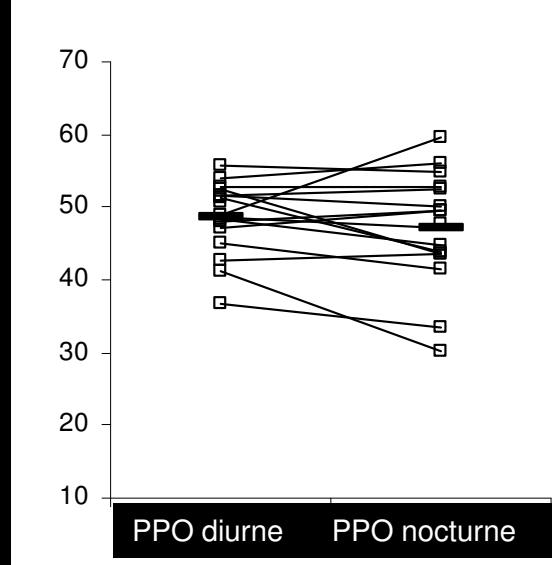
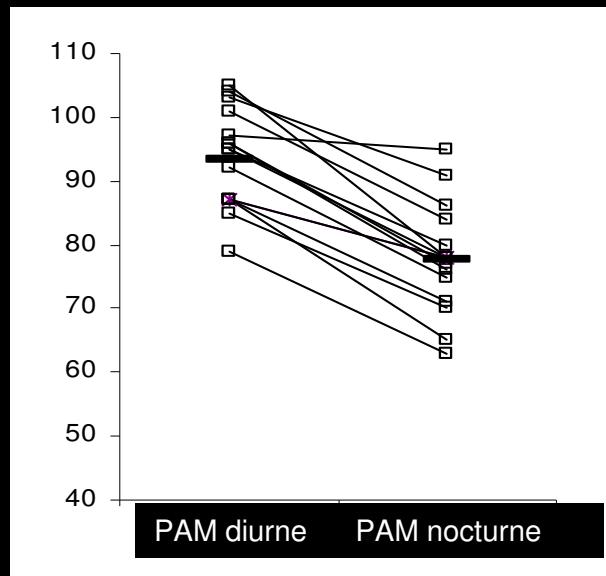


Pression de perfusion oculaire

- Pression artérielle brachiale moins la pression hydrostatique entre bras et œil (=hauteur de la colonne d'eau), moins la PIO

$$PPO = \frac{2}{3} PAM - IOP$$

(PAM=pression artérielle moyenne)

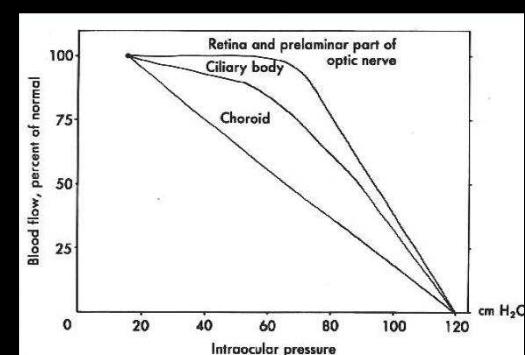
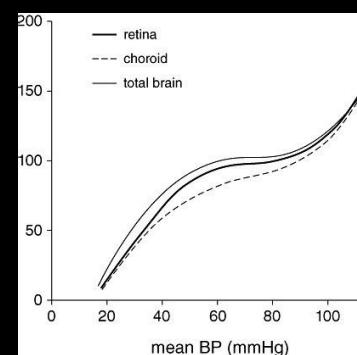
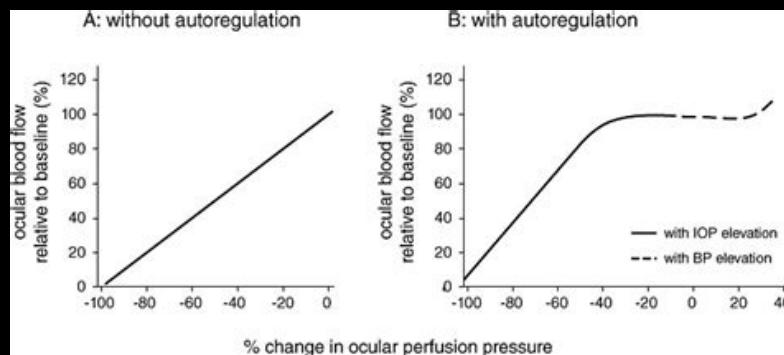


Paques et al
IOVS 2005

⇒ la PPO est autorégulée

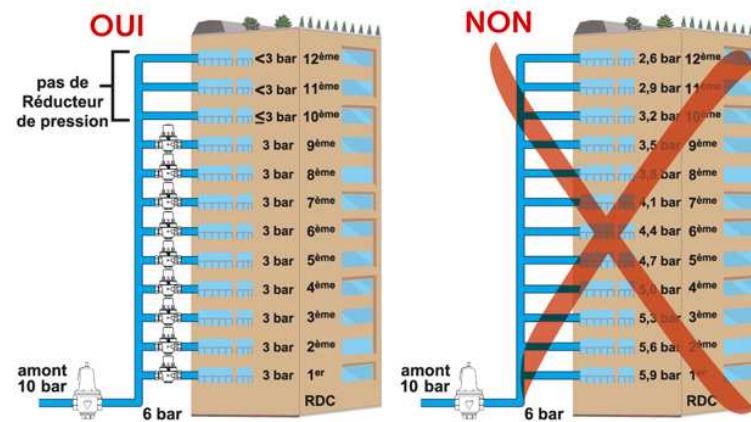
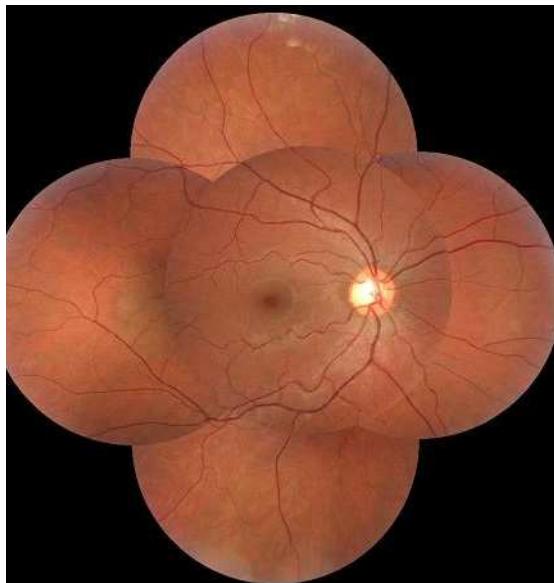
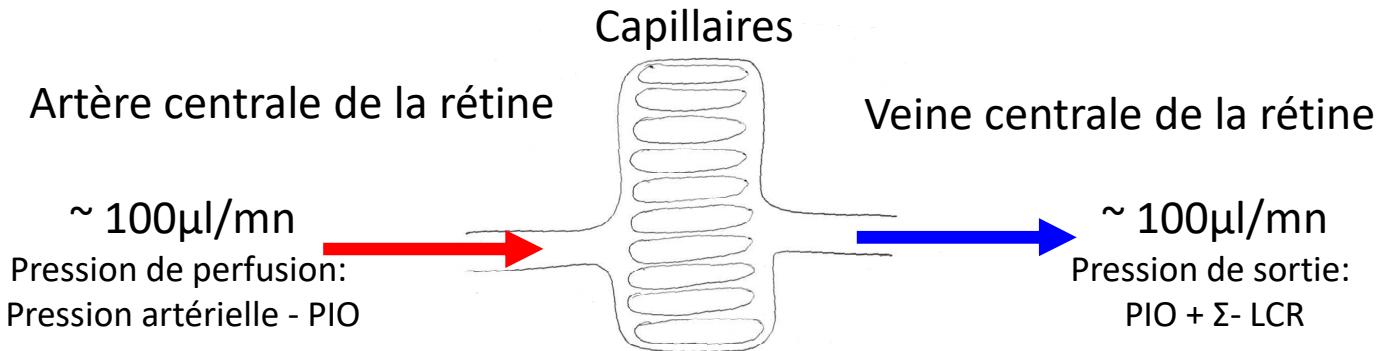
Autorégulation du flux sanguin rétinien

- Capacité des vaisseaux rétiniens à modifier leur diamètre en fonction de divers stimuli pouvant affecter l'apport ou la demande d'O₂
 - pression artérielle
 - activité métabolique
 - variations d 'O₂ et de CO₂
- *Tendant* à maintenir un apport métabolique constant à la rétine interne

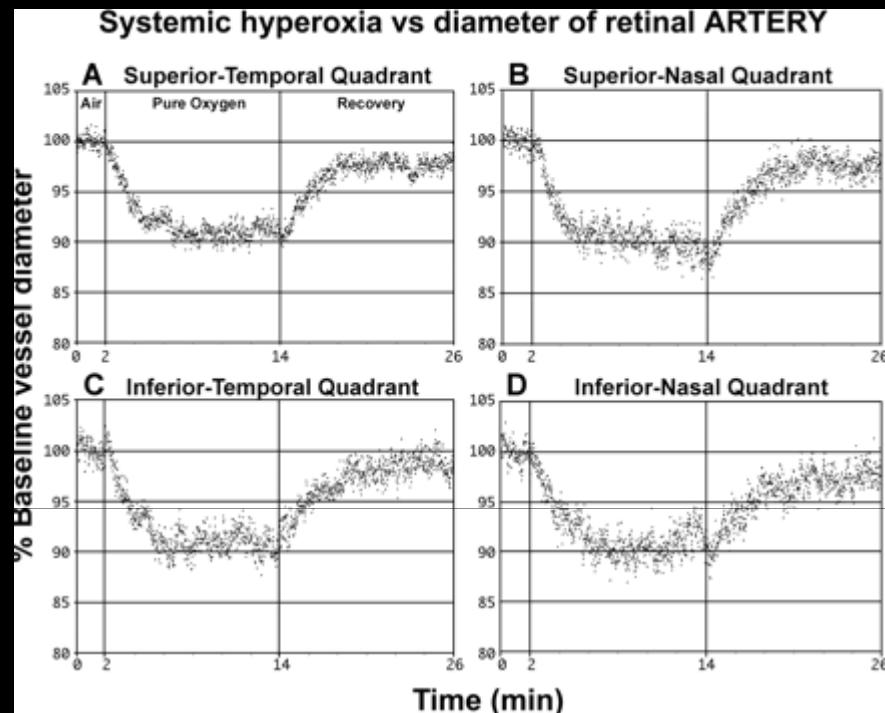


- Tous les vaisseaux rétiniens (des artères aux capillaires aux veinules) contiennent des cellules contractiles, mais pas d'innervation
 - Vasomotricité dépend donc essentiellement de facteurs vasomoteurs endogènes: dérivés de l'endothélium, des cellules gliales et du métabolisme rétinien
 - neurovascular coupling, Shear stress, $[O_2]$, $[CO_2]$, NO, endothelins...
- Loi de Poiseuille : des modifications minimes des diamètres peuvent avoir des conséquences importantes sur le flux
 - Non seulement en aval, mais aussi loco-régional

A single artery irrigates the whole retina
 So how does the retinal circulation achieve uniform perfusion?



L'oxygène constricte les vaisseaux rétiniens



Seendy et al, IOVS 2005

- Autorégulation des vaisseaux rétiniens
 - ↘ PaO₂ : vasodilatation
 - ↗ PaO₂ : vasoconstriction (rôle de l'endothéline)
 - ↗ CO₂ : vasodilatation

Le couplage neurovasculaire rétinien

- = vasodilatation induite par la demande métabolique neuronale
- Dans le cerveau: mesurée par Blood oxygen dependent level (BOLD) functional magnetic resonance imaging (fMRI)
- Dans la rétine: mesure du calibre vasculaire avant et après stimulation lumineuse intermittente ($\pm 15\text{Hz}$)
Normale: vasodilation 3%-5%

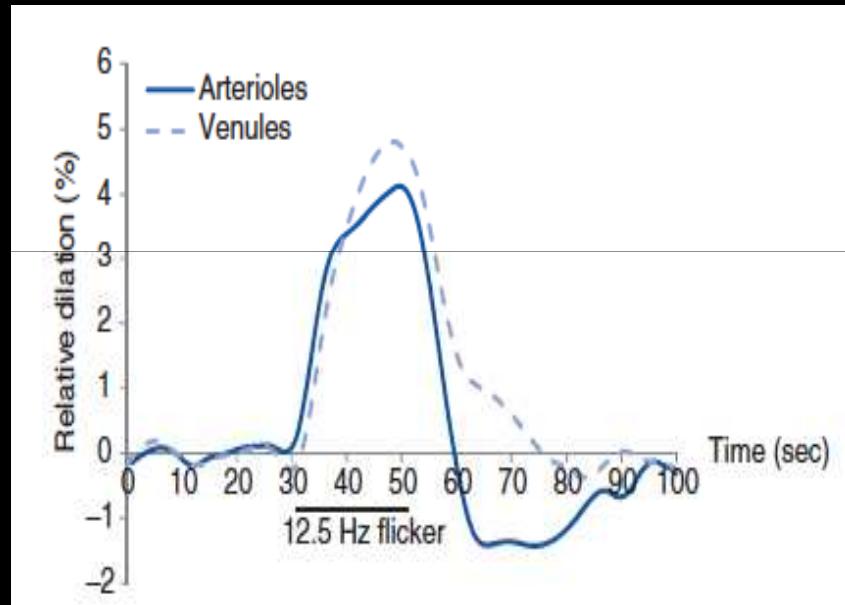
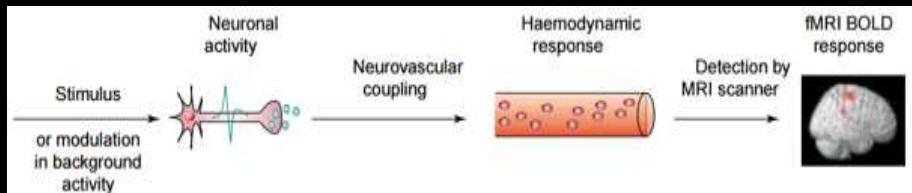
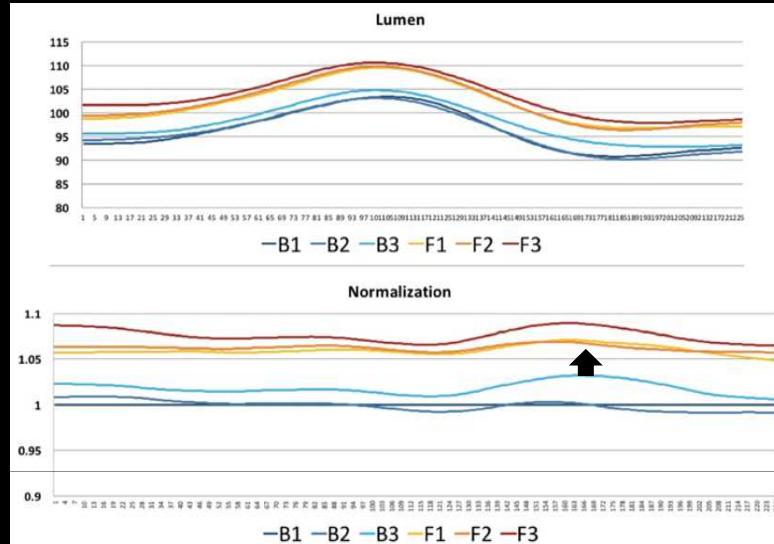
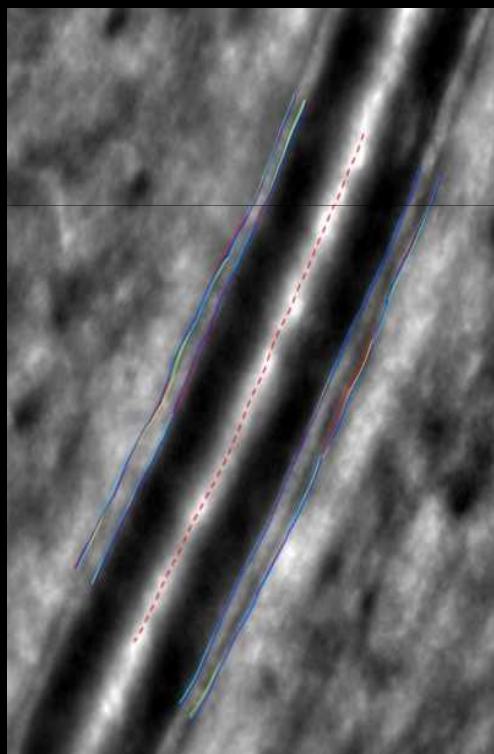
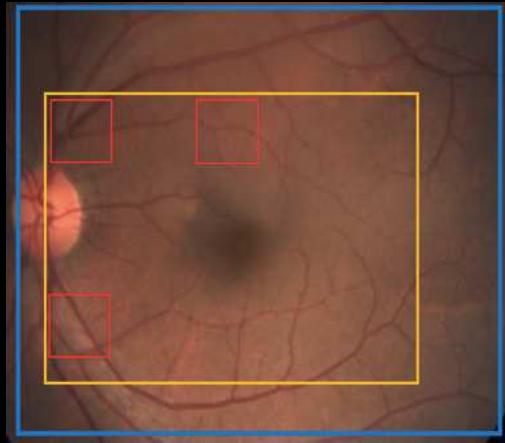


Figure 2. Human retinal arteriole and venule relative dilations in response to 20 s of 12.5 Hz luminance flicker.

Newman EA. 2015 Glial cell regulation of neuronal activity and blood flow in the retina by release of gliotransmitters. *Phil. Trans. R. Soc. B* 370: 20140195.

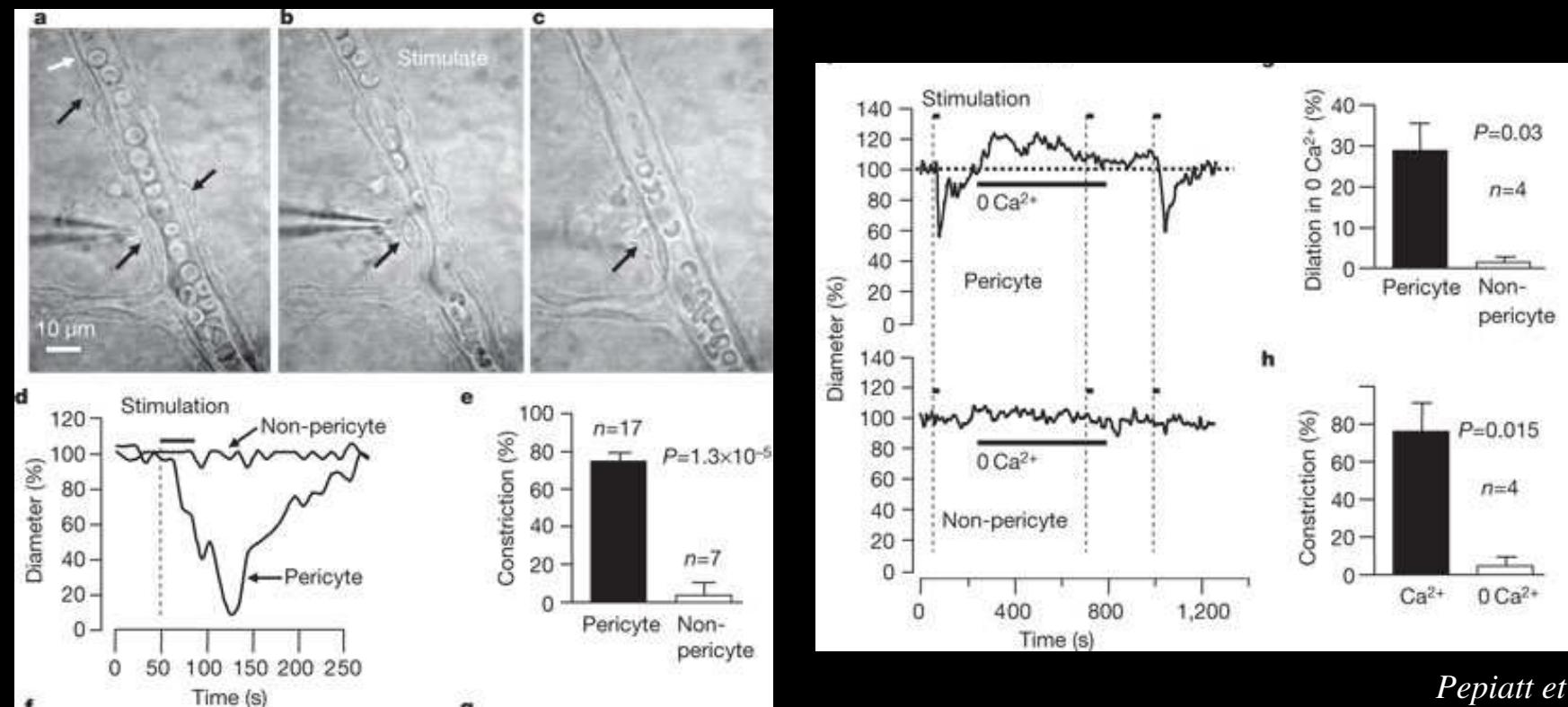
Noonan, J. E., Lamoureux, E. L. and Sarossy, M. (2015), Neuronal regulation of retinal blood flow. *Clin Experiment Ophthalmol*, 43: 673-682



AOV - Healthy subjects (n= 23)						
	B2	B3	F1	F2	F3	
Ratio/B1	-0.09 (±1.56)	+0.39 (±1.22)	+3.31 (±1.91)	+3.16 (±2.01)	+3.05 (±2.62)	
Average Basal	+0.15 (±1.15)					
Average Flicker				+3.17 (±2.18)		

D Castro-Farias

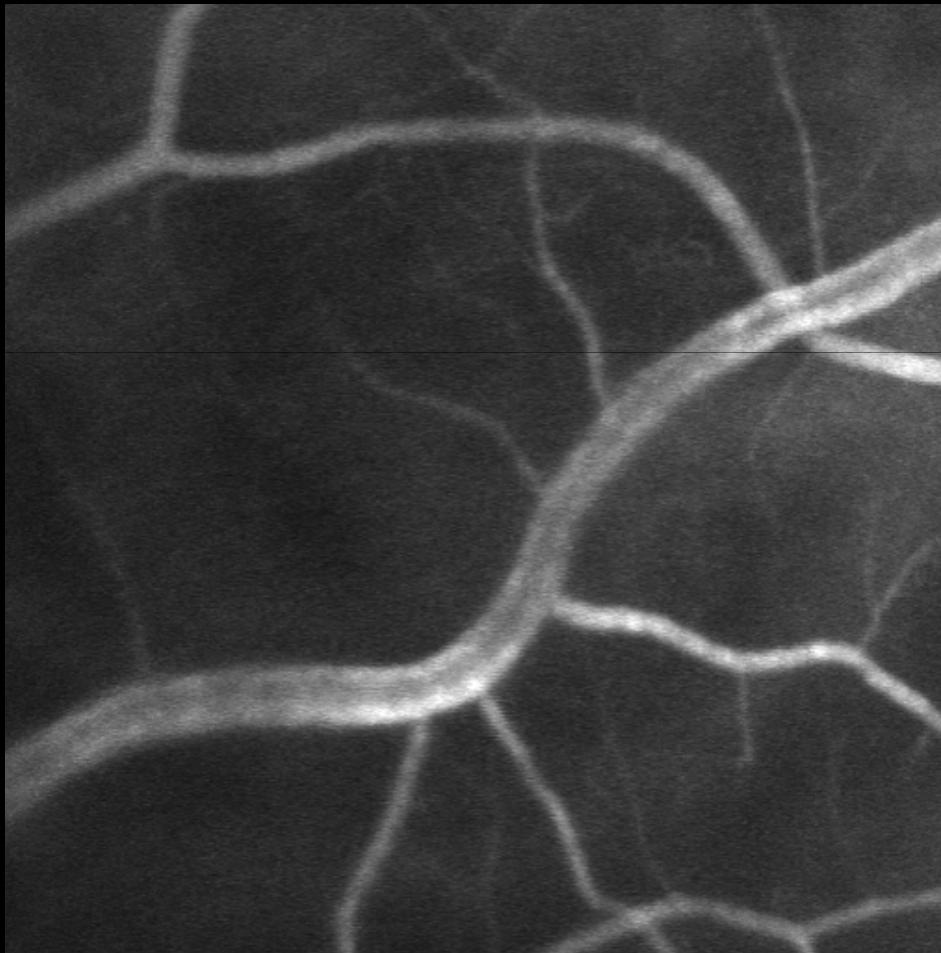
Pericyte (probably) control capillary flow



Pepiatt et coll
Nature 2006

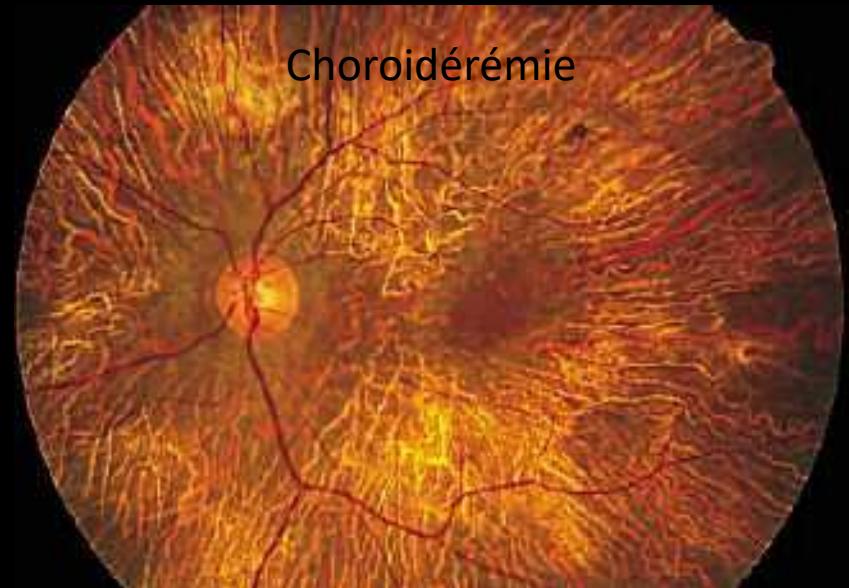
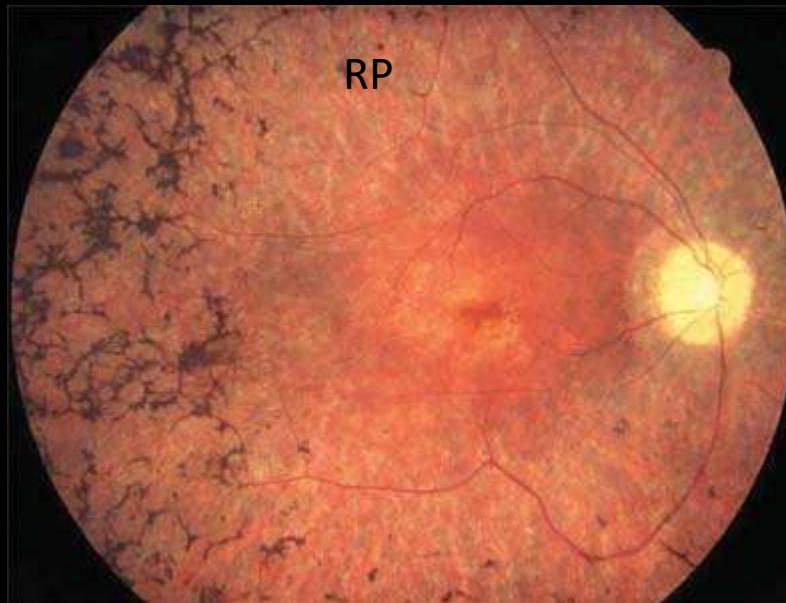
- Le diamètre vasculaire artériel est donc la résultante de 3 processus dynamiques:
 - Le réflexe myogénique qui équilibre la tension *pariétale*
 - Le « shear stress » qui équilibre le shear stress *endothélial*
 - Le couplage neurovasculaire qui s'ajuste aux besoins des *neurones*

Interaction between IOP and blood flow: velocity of venous flow increases with IOP

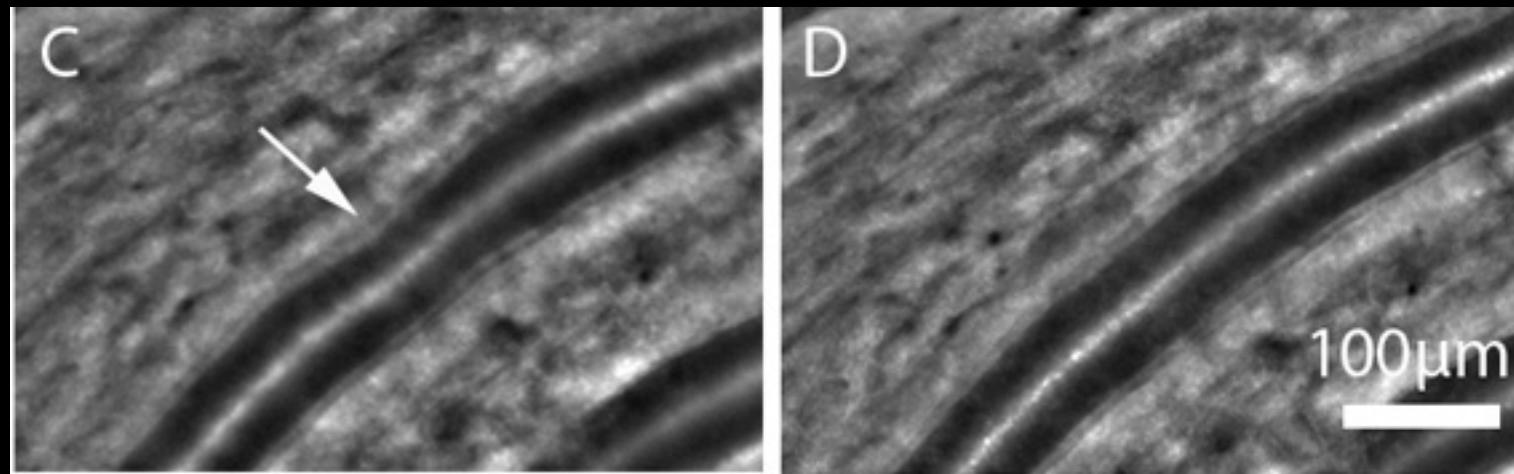
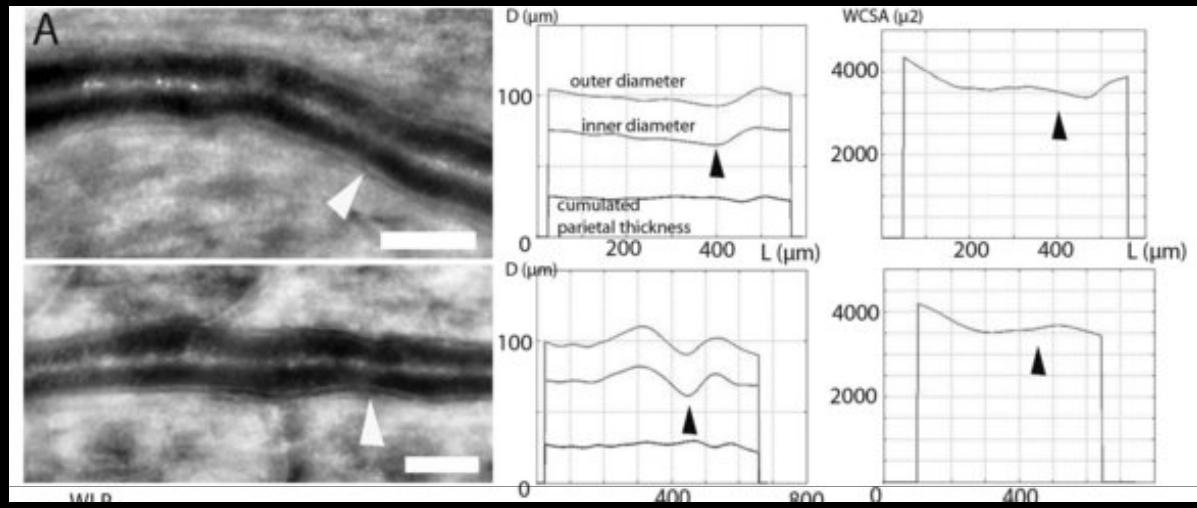
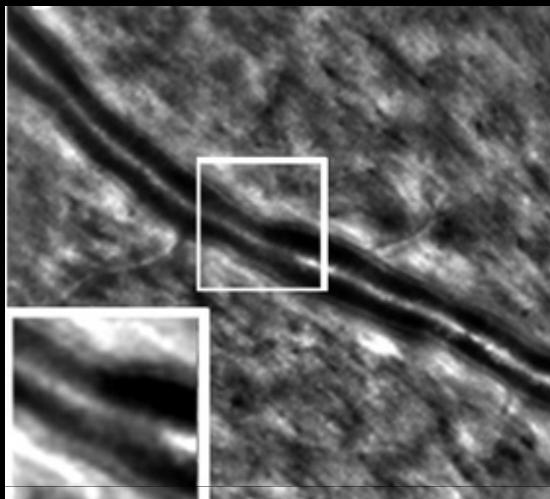


Vasoconstriction rétinienne au cours des rétinopathies pigmentaires

- La RP entraîne une disparition des photorécepteurs, et donc une meilleure diffusion de l'oxygène venant de la choroïde vers la rétine interne
- Cette hyperoxygénation permanente active l'autorégulation vasculaire, d'où une vasoconstriction
- Cette vasoconstriction est moins marquée en cas d'atrophie associée de la choriocapillaire



FAN: a focal increase of arteriolar tone?



Vascular aging

Le croisement artéioveineux pathologique

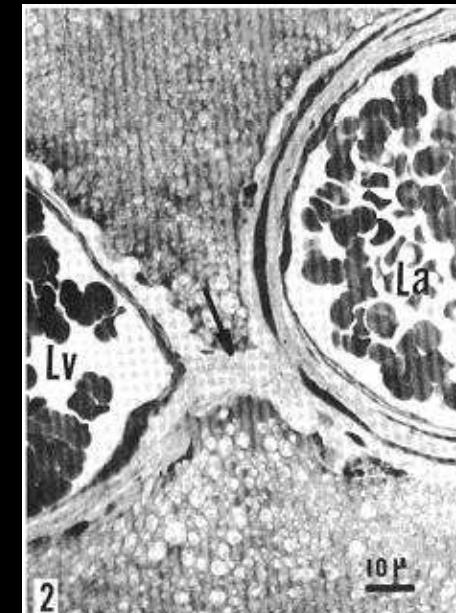
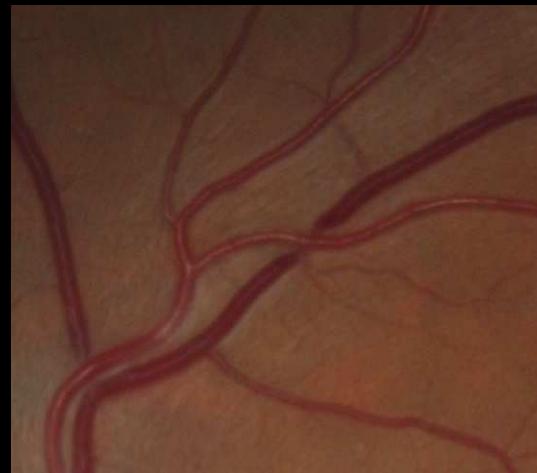
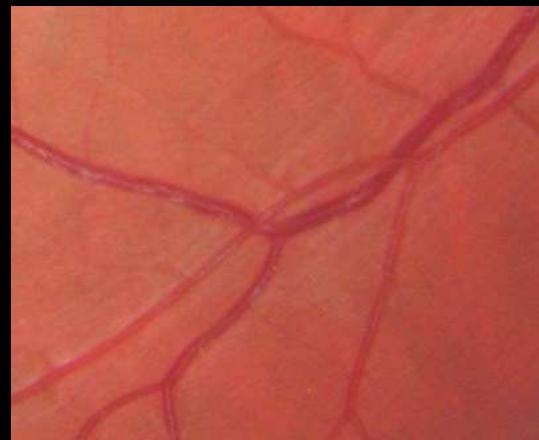
= modification de calibre ou de trajet de la veine à proximité de l'artère

Croisement artère sur veine dans la majorité des cas

Présence de fibres adventicielles communes

solidarisant artère et veine à ce niveau

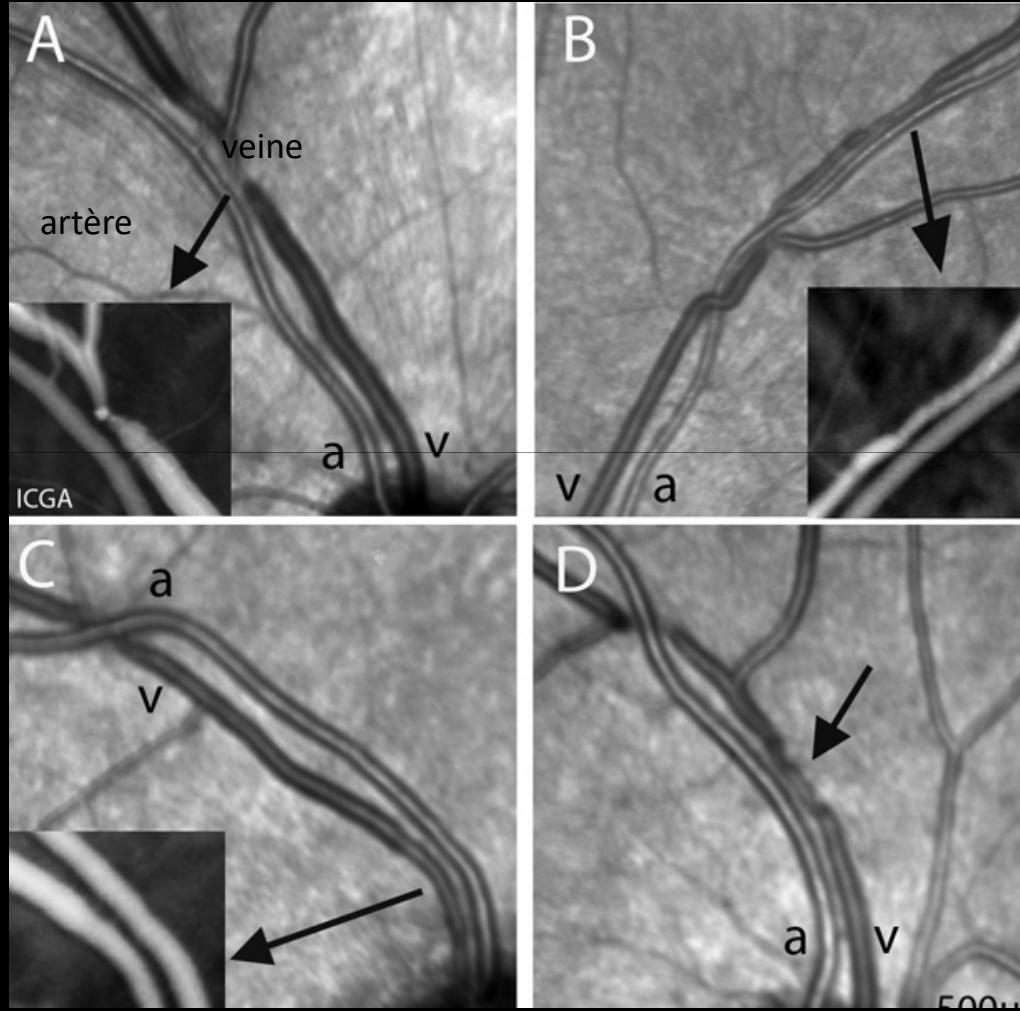
Le croisement AV exerce une contrainte mécanique orientant la tortuosité veineuse



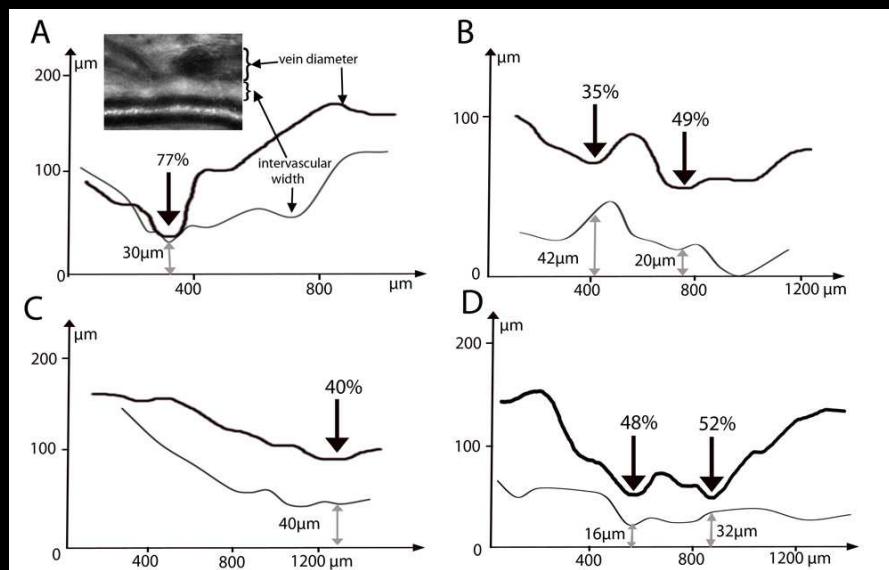
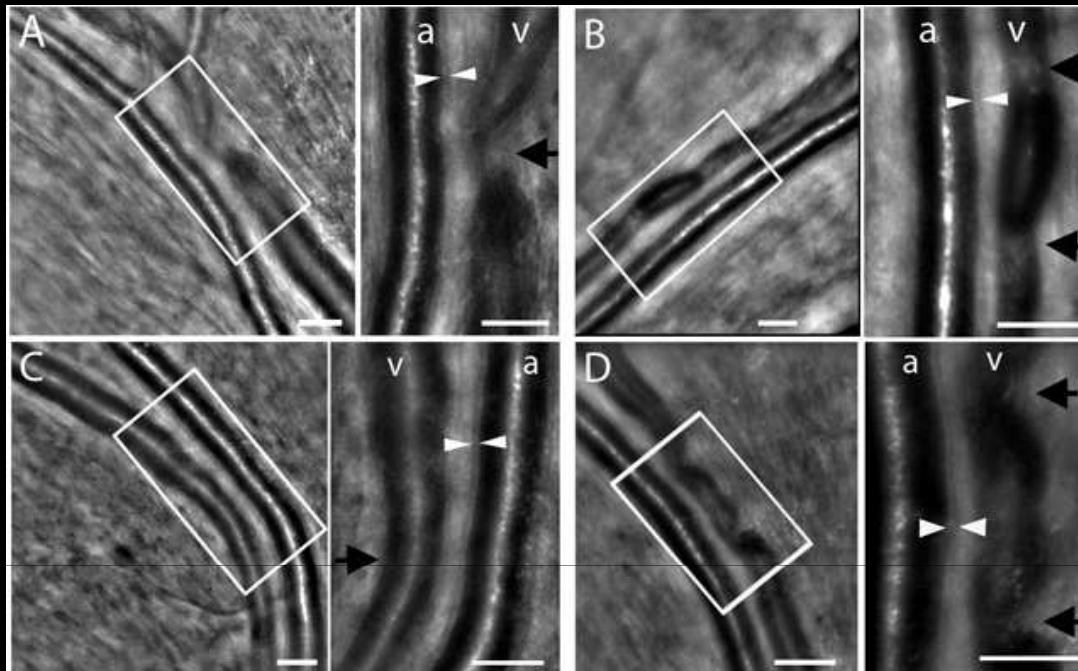
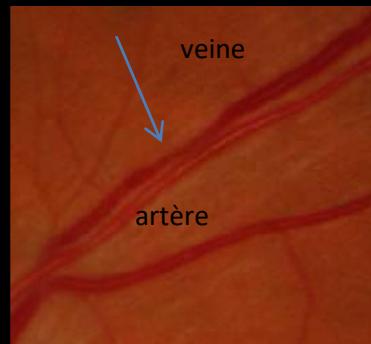
Adventice commune:
Fibres solidarisant l'artère et la veine
aux croisements AV

Le signe du croisement peut se voir... sans croisement

68



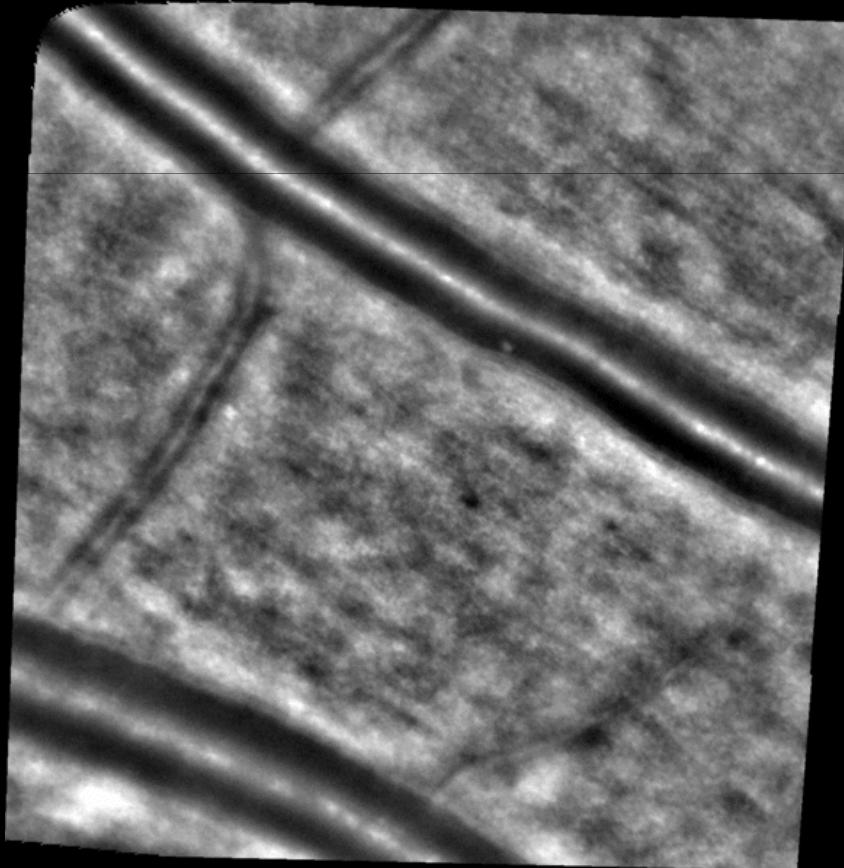
Analyse morphométrique fine de « signes du croisement » sans croisement



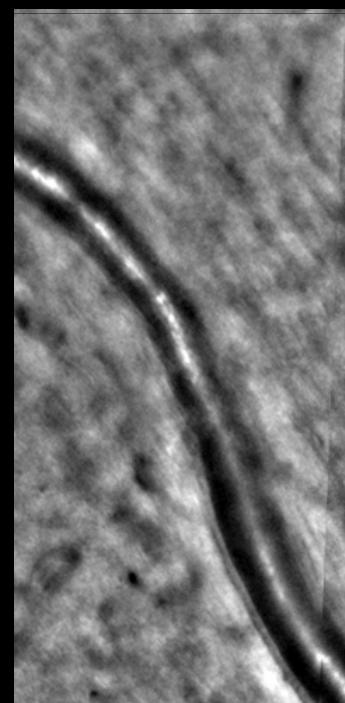
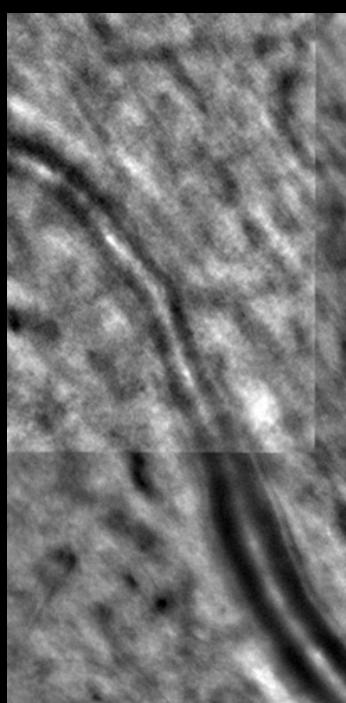
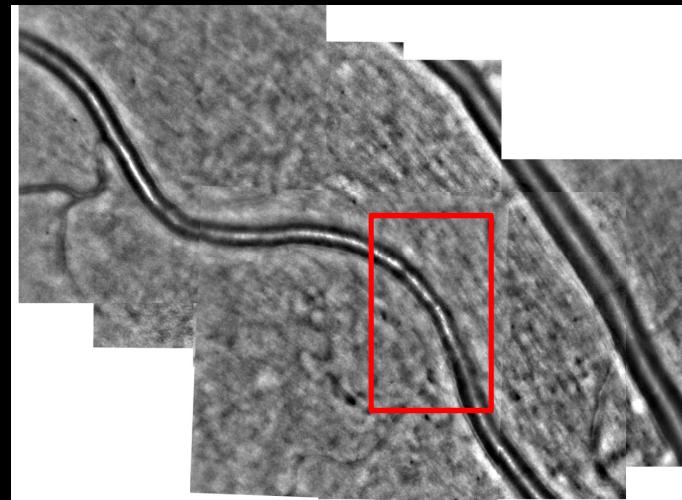
Dr Aurélie Brolly

Arterial vasomotricity

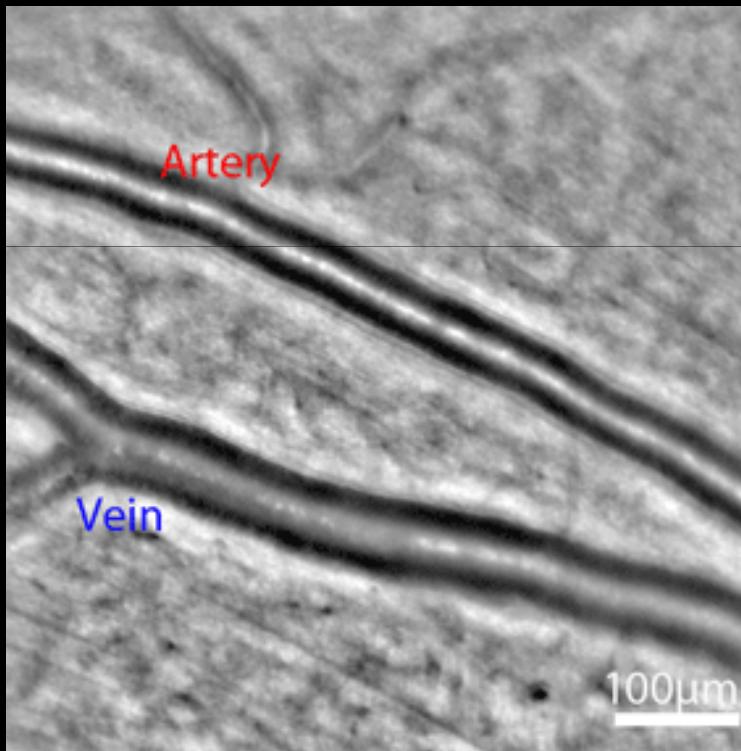
- Patient avec rétrécissement focal suivi toutes les semaines
- Apparition d'une dilatation lors du suivi sans modification de traitement



Kidney disease (IRIR study, Dr Faure, Caen)

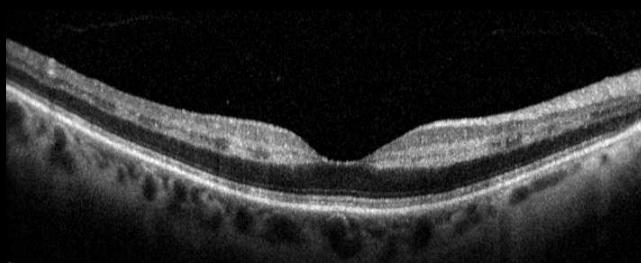
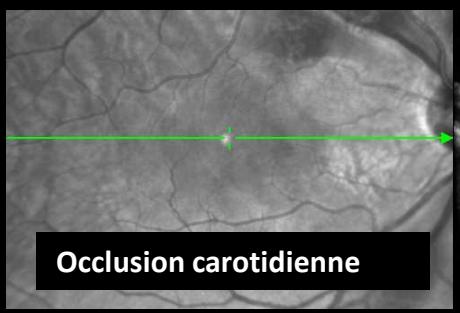
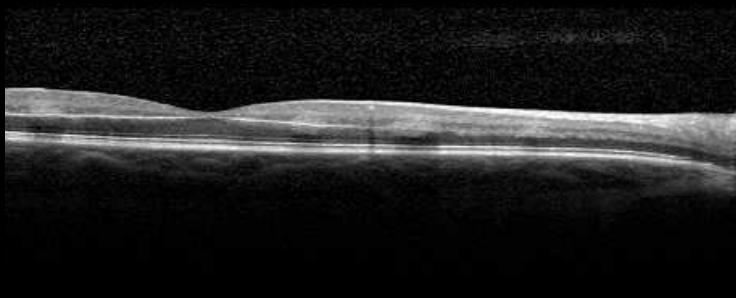
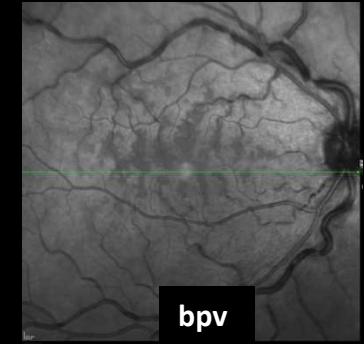
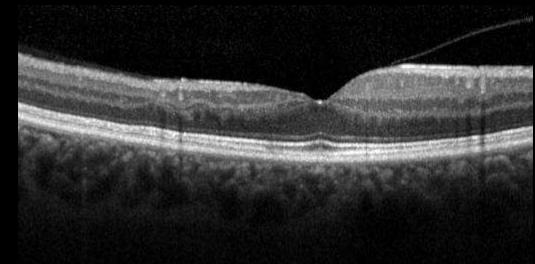
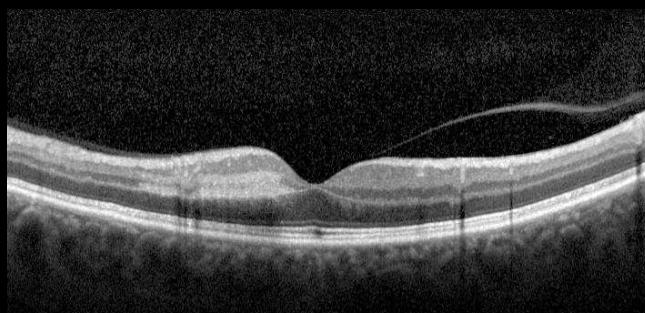
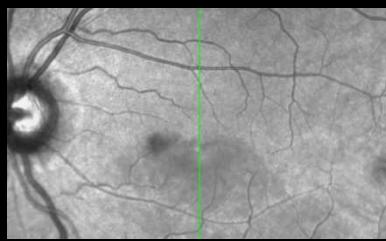
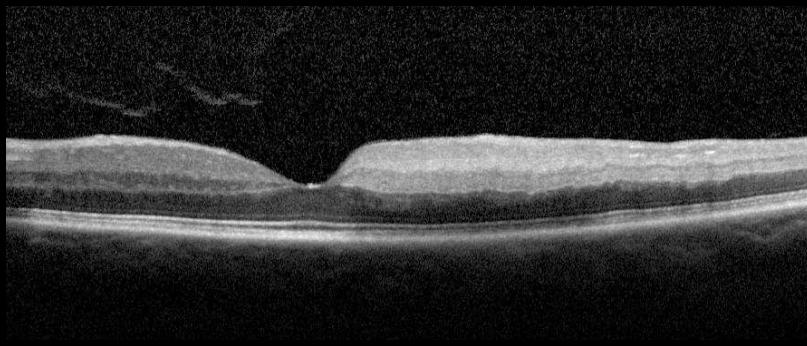
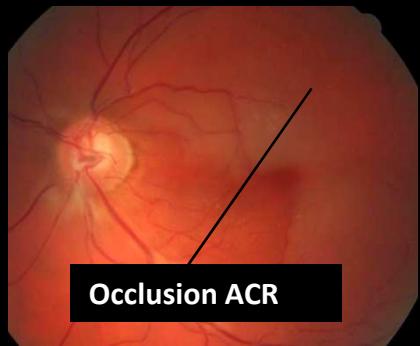


2 years follow-up of a patient with kidney disease

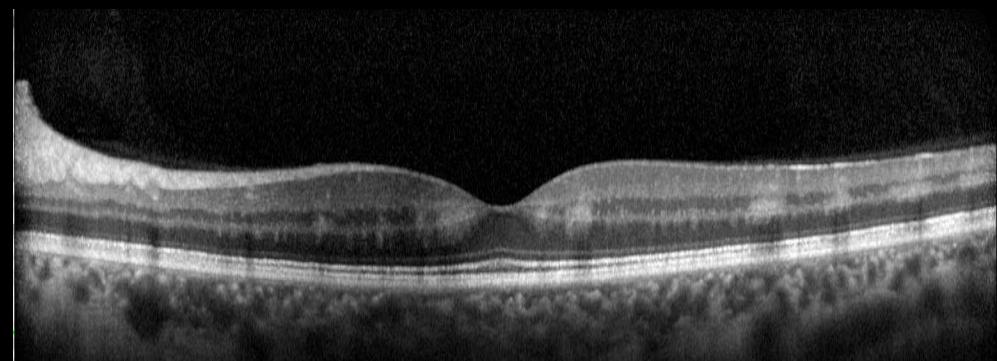
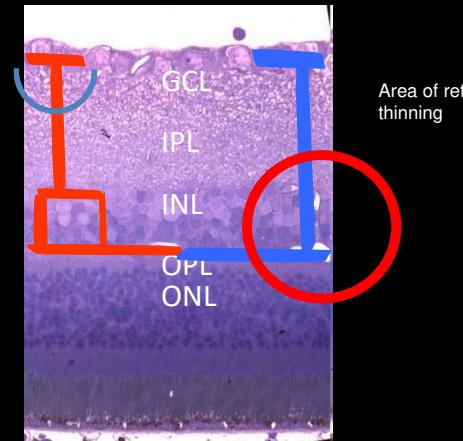
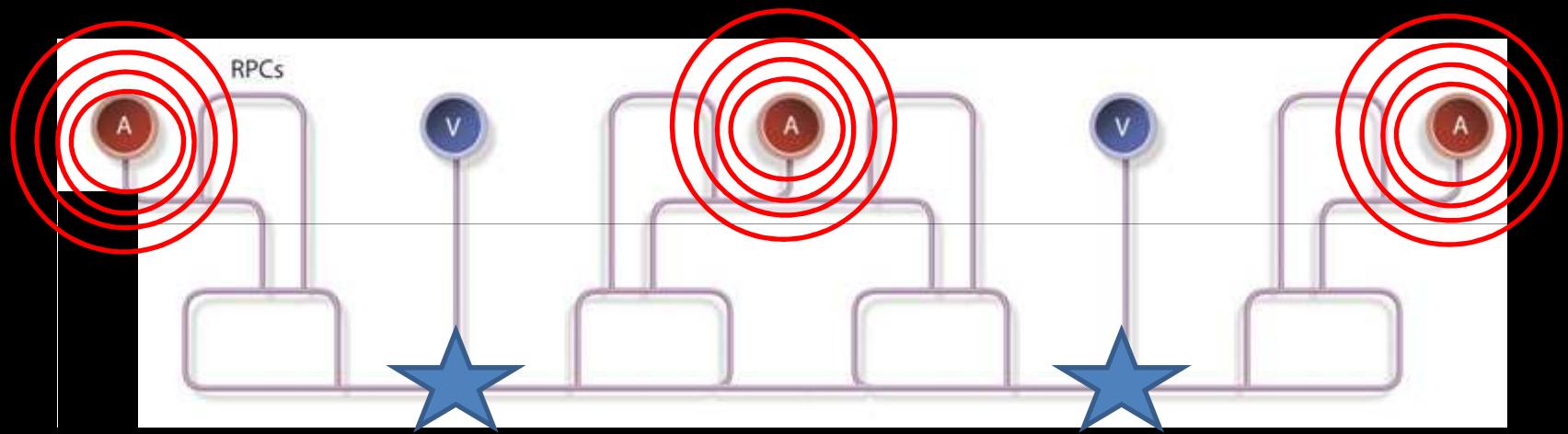


Dysfonction vasculaire:

- bas débit rétinien
- vasoconstriction

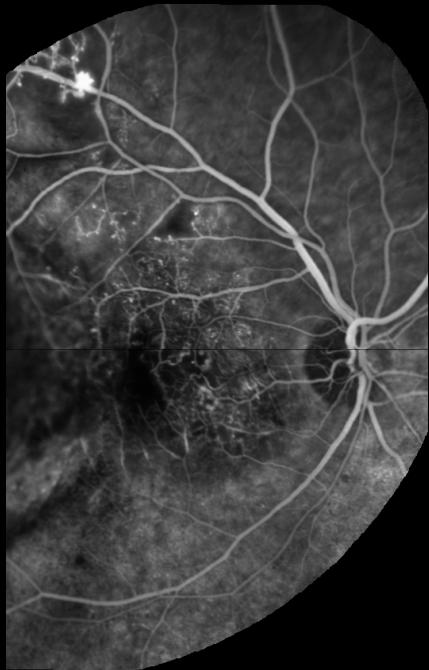


Effect of decreased perfusion pressure on retinal metabolism: The microvascular anatomy explains the localisation of perivenular whitening (« PAMM »)

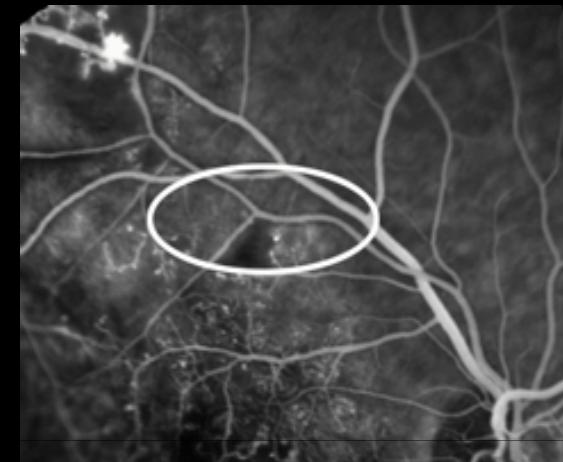
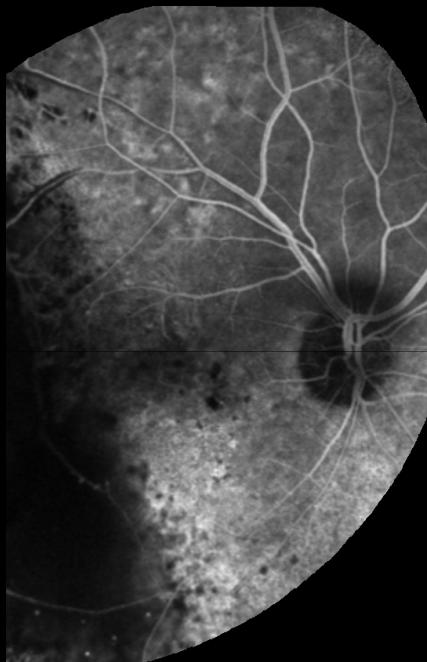


Progressive arterial and venous constriction following proton therapy for ocular melanoma

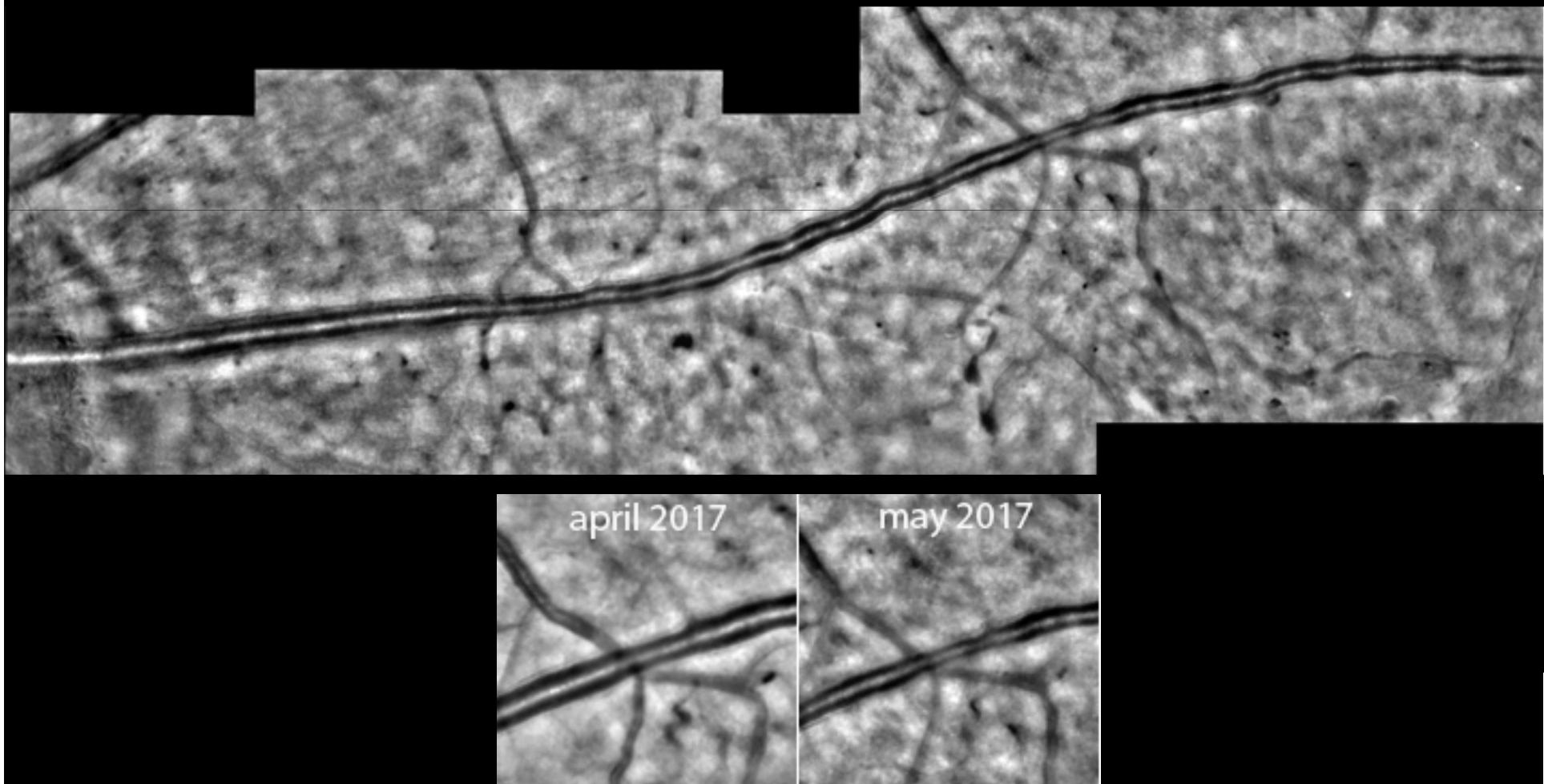
2014



2017



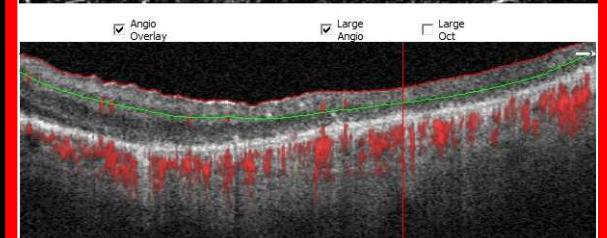
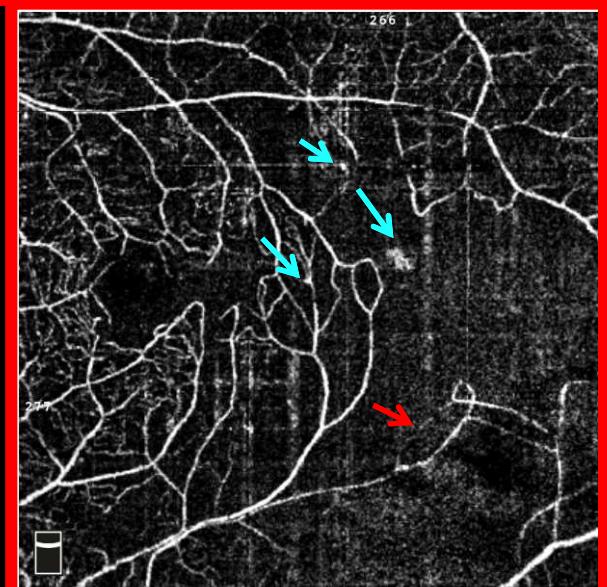
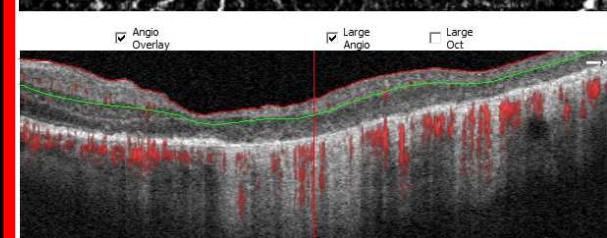
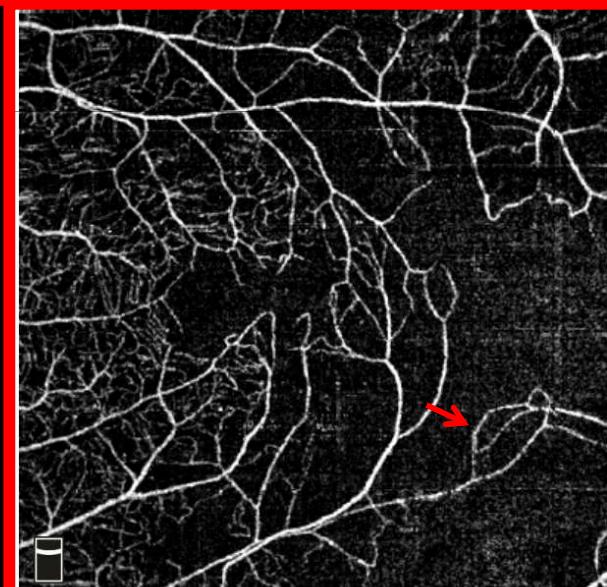
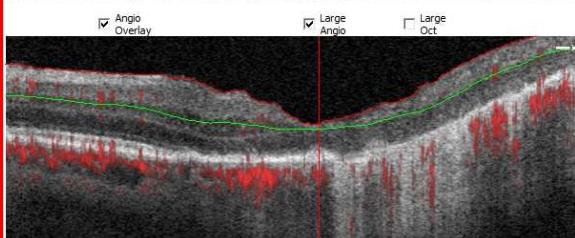
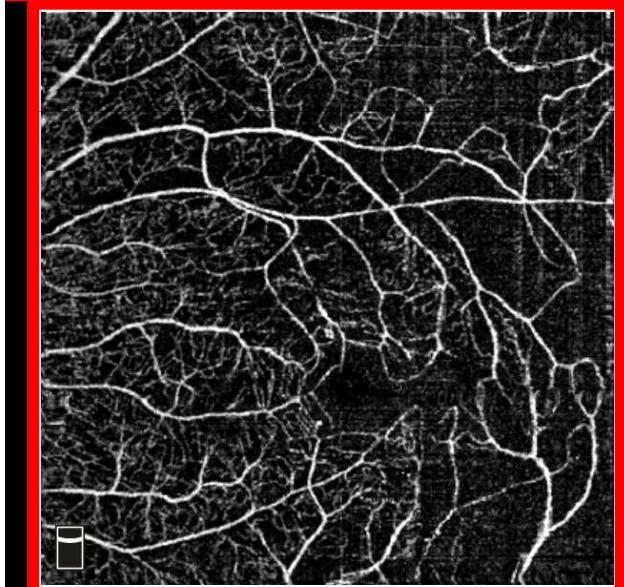
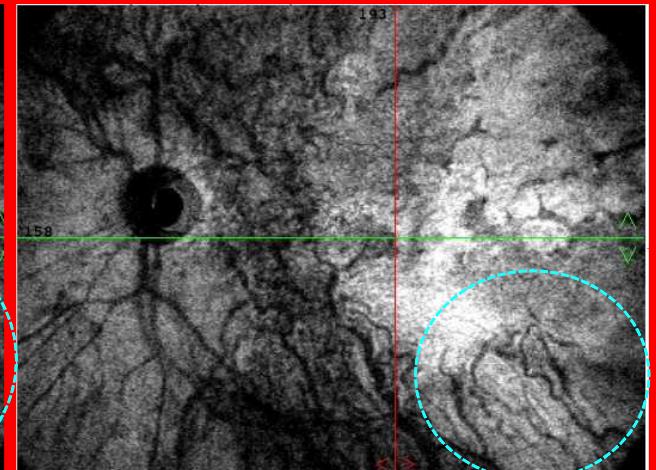
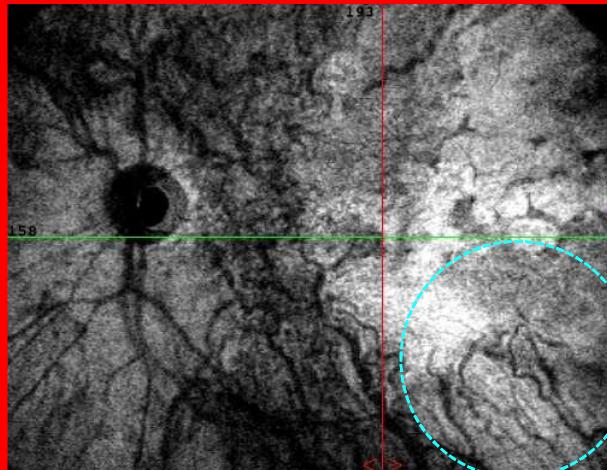
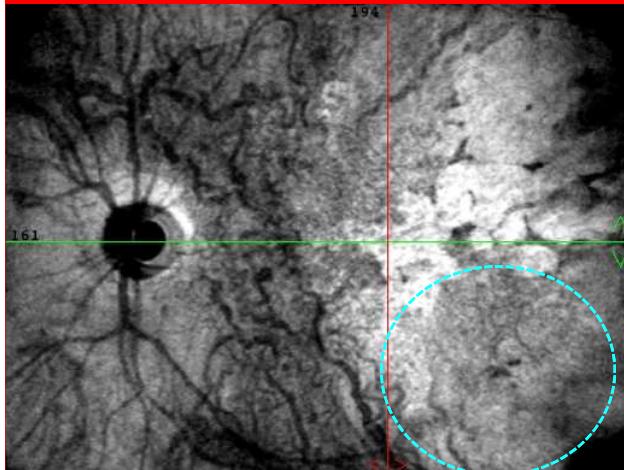
Evolution of arterial vasoconstriction



16/06/2017

25/07/2017

05/09/2017



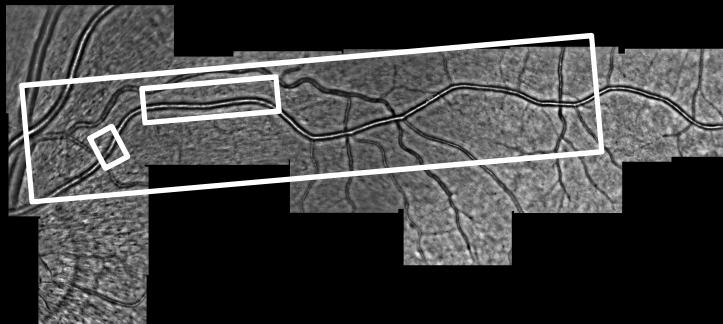
What The Future?

Projects

- Clinical investigations: vascular dynamics, Laser Doppler holography (Michael, Leo), in vivo sectioning (Pedro, Kate)
- PhDs: Iyed Trimeche, Laureline Julien (exp), Sophie Bonnin
- Histology of the entire vasculature of the human eye(HistoParis)
- Oxymetry (EyeWin project, Cyril Petit)
- Clinical therapy

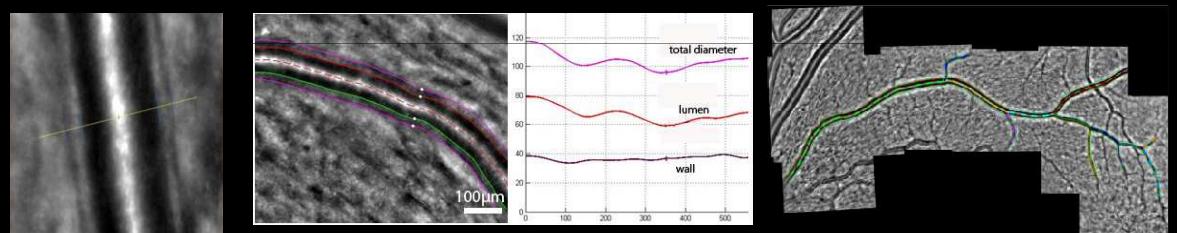
Clinical explorations of vessels using the rtx1

Qualitative analysis

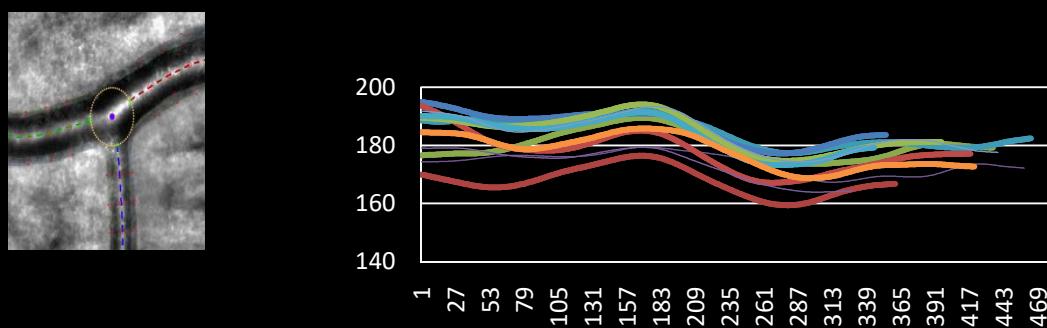


Parietal thickness

- Point measurements
- Segments
- Montages

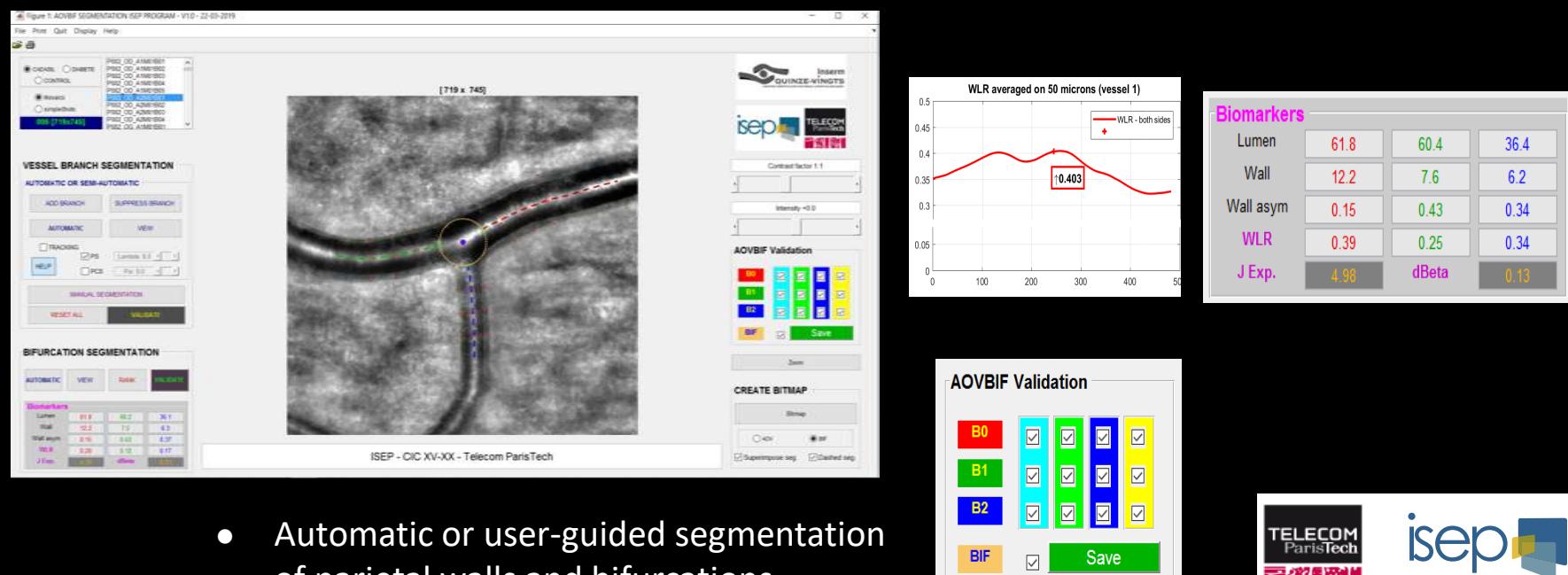


Branching coefficients



Neurovascular coupling

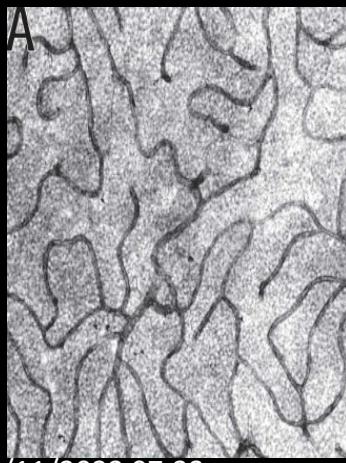
- AOVBF Software framework for the segmentation of retinal arteries in AOO images and biomarker measures
 - New methodological contributions:
- Artery wall segmentation using deformable models with parallelism constraint: better robustness to noise and lack of contrast (Rossant et al., 2015)(Lermé et al. 2016)
- Refinement at bifurcations, with locally adaptive parameters, depending on distance to the junction and angles between branches (submitted to IEEE. ICIP'19)
- Automatic biomarker calcul derived from the segmentation results (*wlr*, branching coefficients, morphograms, etc.)
- No equivalent in the literature
 - operator-dependent software (Arichika et al, 2016)



Evolutions futures

■ AO-OCT

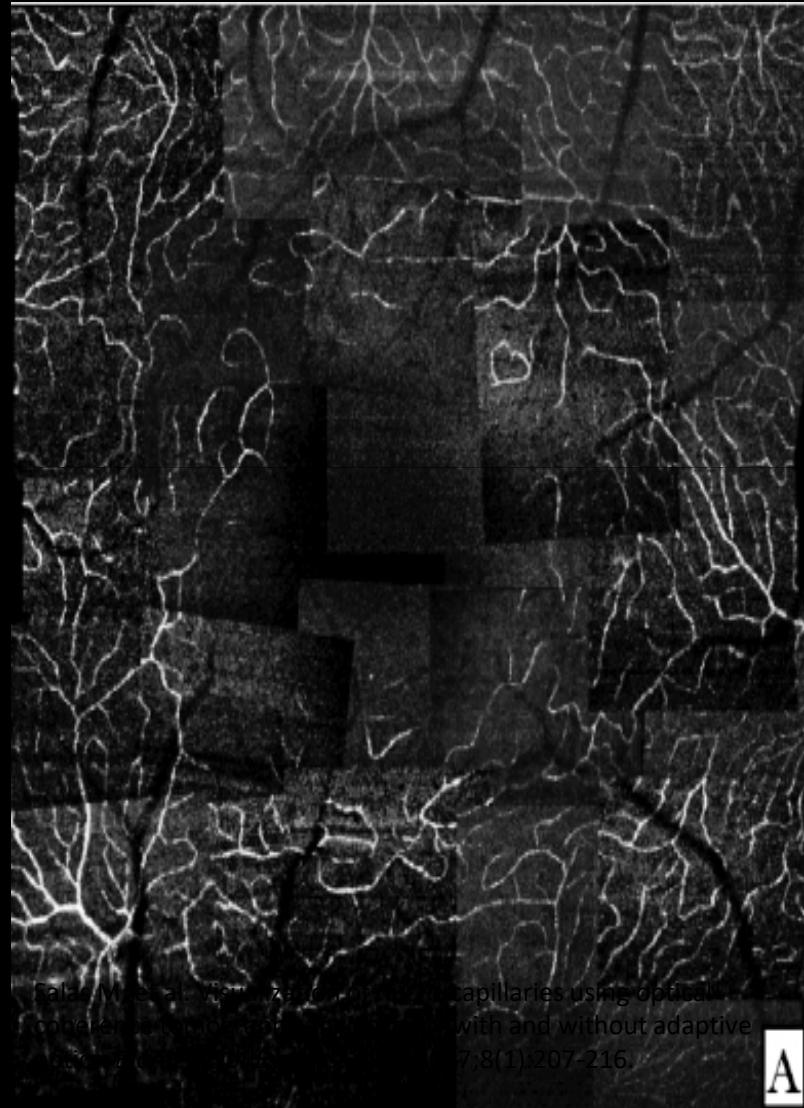
- FAMOS European project (Prof W Drexler, University of Vienna)
- 1-2 μm resolution
- confocal segmentation
- simultaneous B scan registration
- 200 KHz



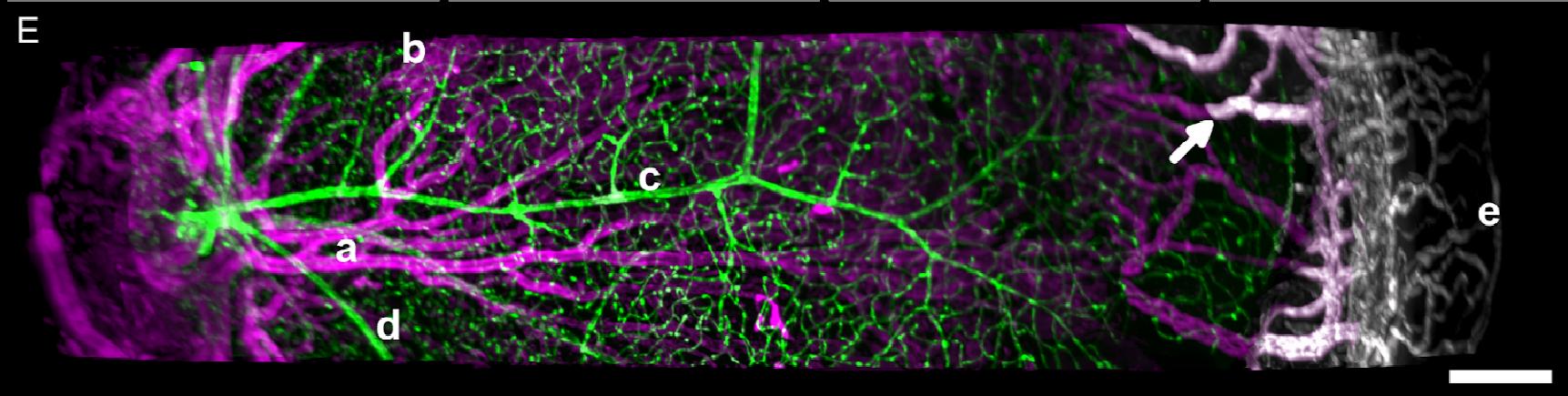
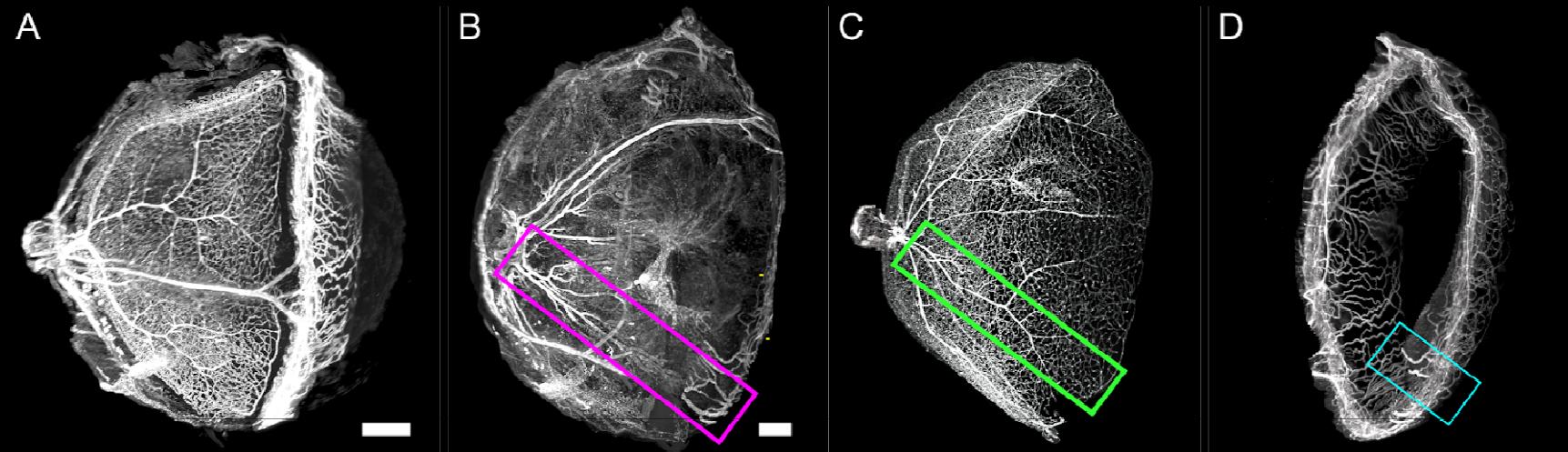
26/11/2022 07:33

Chan G, et al. IOVS
2012;53(9):5502-5514

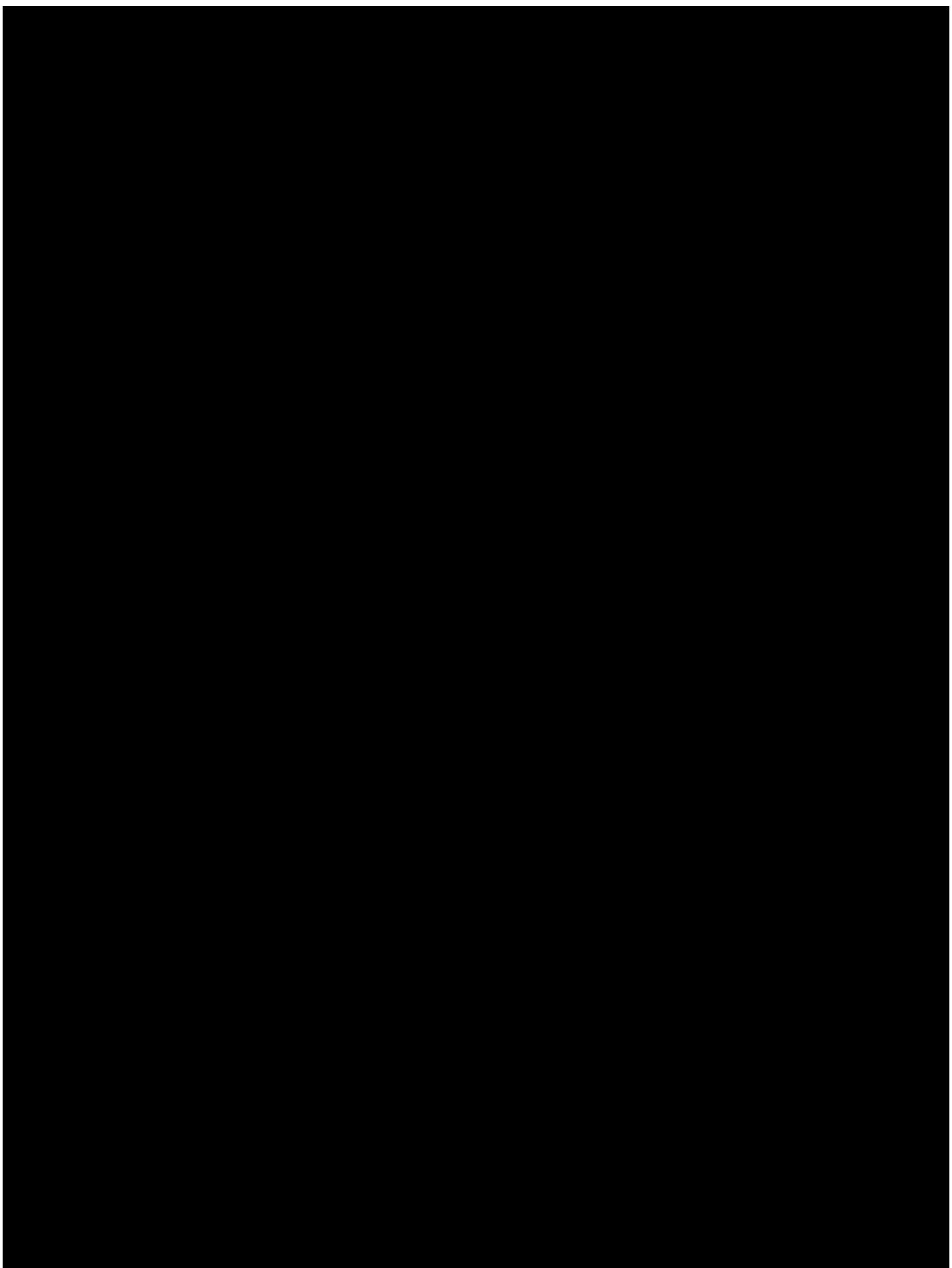
Hôpital Lariboisière Ophtalmopôle de Paris

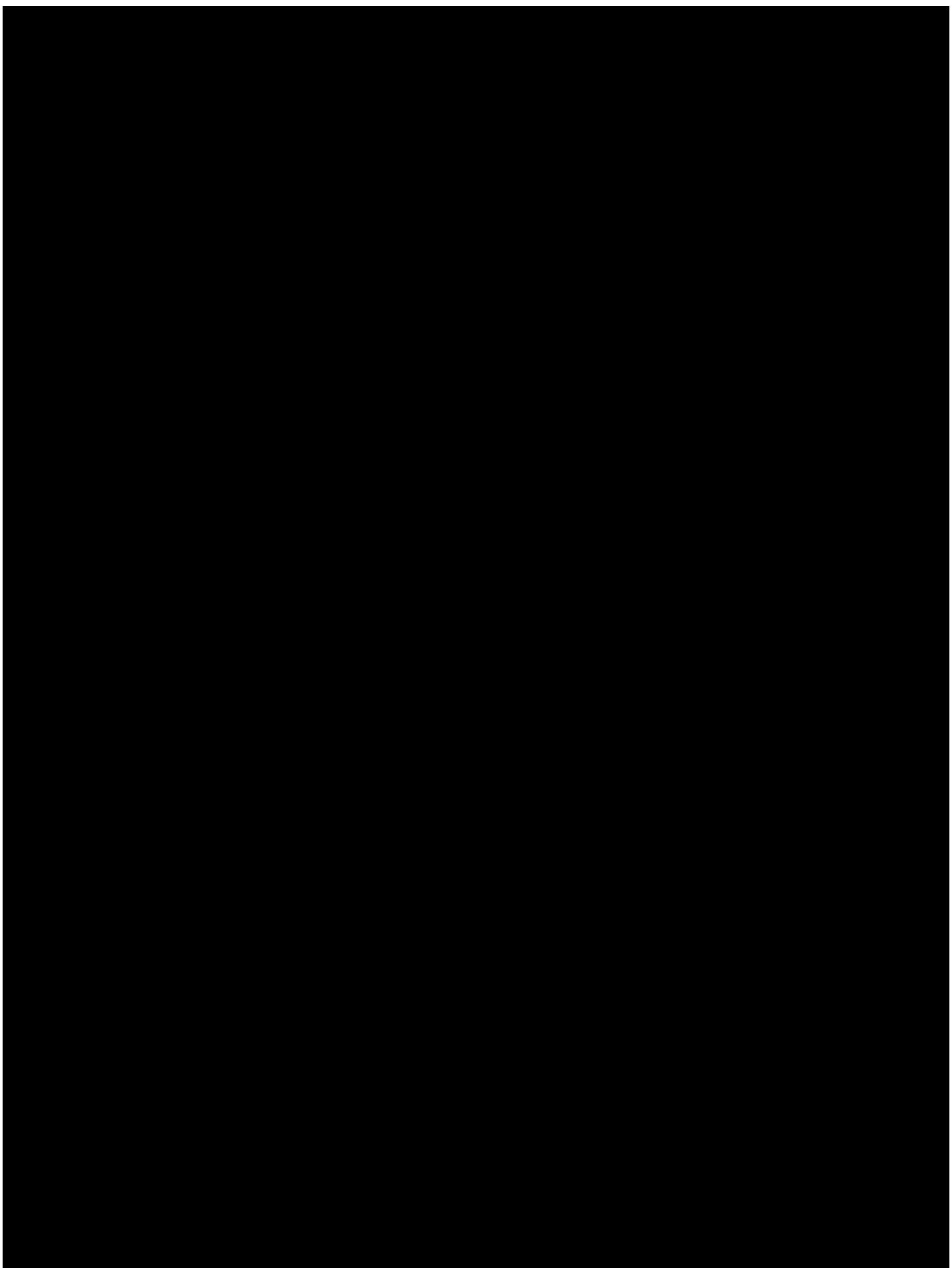


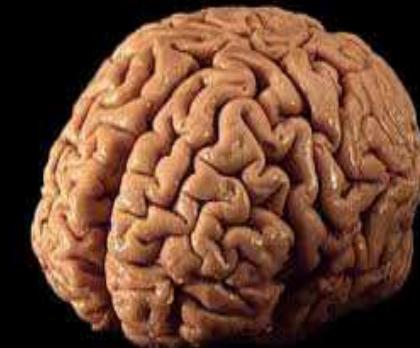
histology



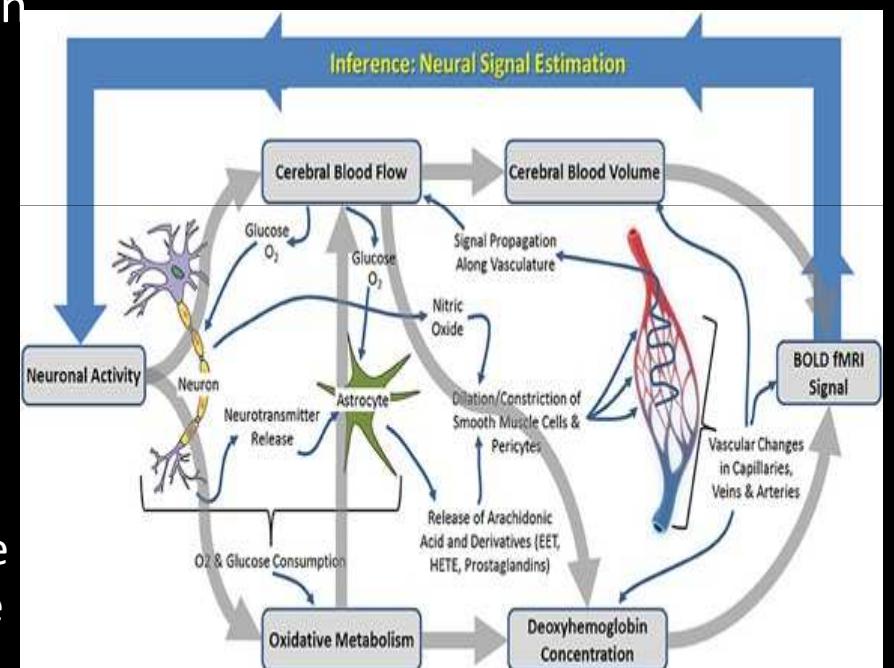
Merci de votre attention





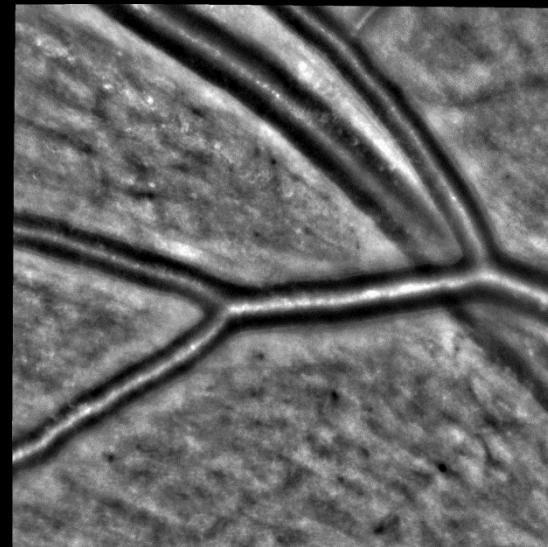
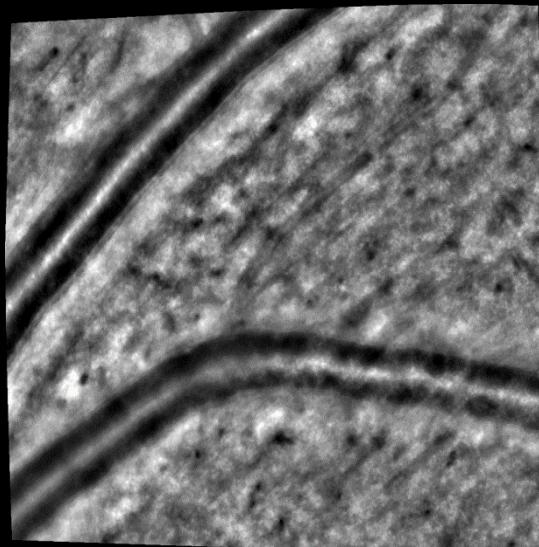


- Functional Hyperemia in the brain
 - Neuron activity leads to local increase in blood flow
 - =Neurovascular coupling (NVC)
 - Two mechanisms possibly involved in vasodilation
 - » Secondary to O₂ depletion (feedbackward)
 - » Stimulation by neurons (feedforward)
 - Mediators: CO₂, H⁺, K⁺, lactate, glucose, adenosine, nitric oxide (NO), glutamate



Crédit C. Martin

- Flickering light stimulation in the rtx1 camera
 - Luminic on/off stimulation cycle
 - Yellow light (570 nm)
 - $29^\circ \times 20^\circ$ rectangle light stimulation area
 - $4^\circ \times 4^\circ$ acquired image
 - Frequency: 15 Hz
 - Timing: 20 s



A rajouter

- Moderniser histologie capillaires rétiniens, incluant microglies
- Imagerie OA capillaires
- Interaction avec neurones
- Débit sanguin rétinien relatif
- Désaturation oxygène rétine
- Dark current