

Œil et Hypertension artérielle:

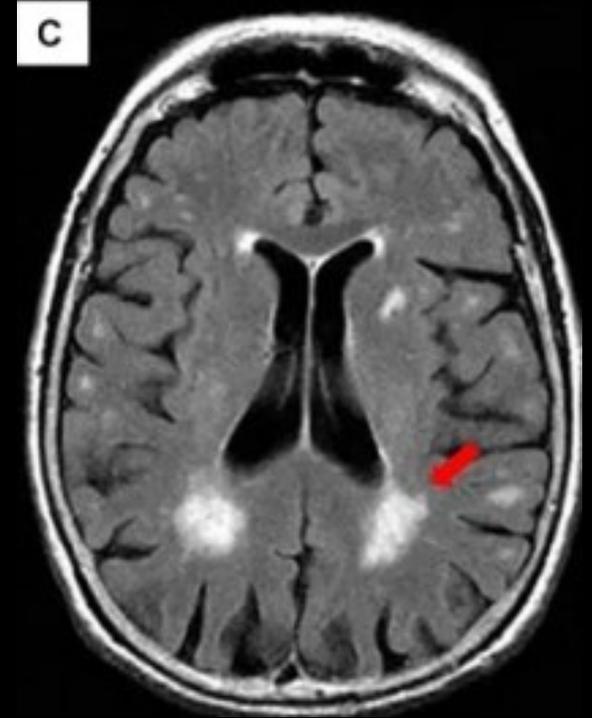
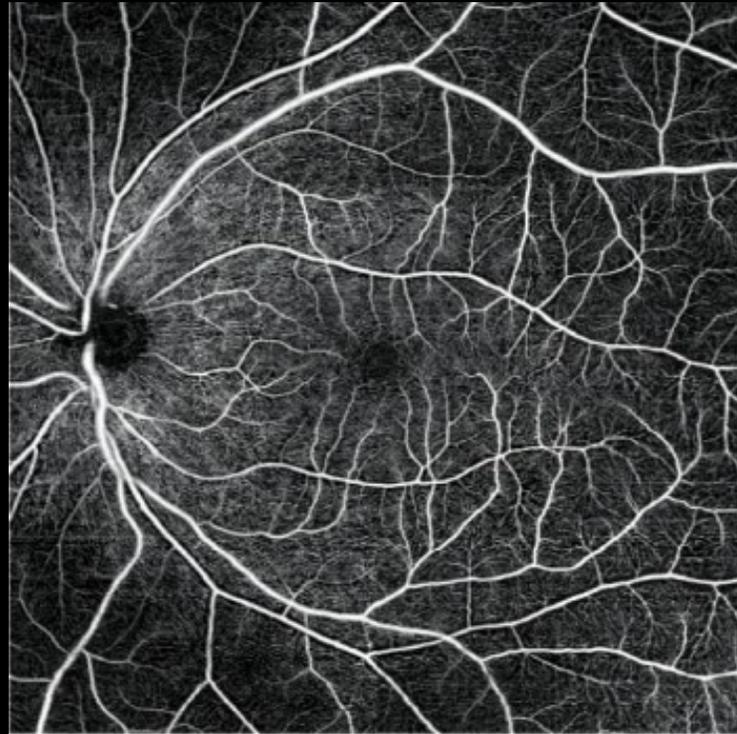
Nouveaux aspects

Clément Gratiot, Rana Saad, Céline Chaumette, Florence Rossant, Céline Faure, Michel Paques

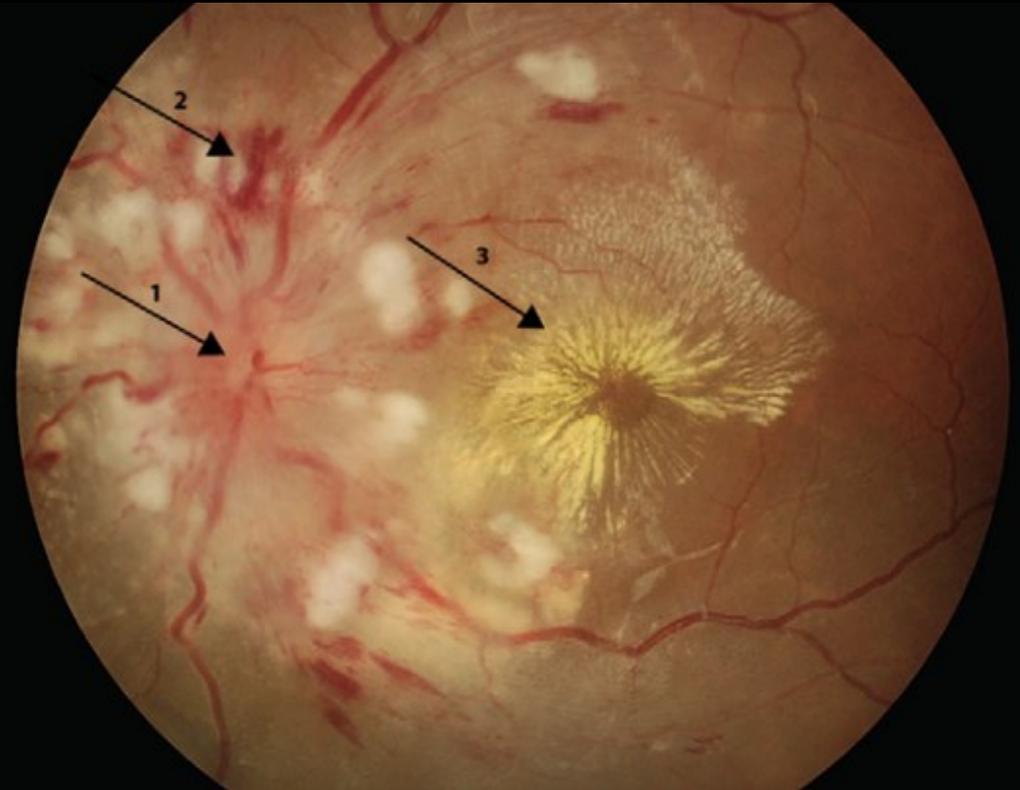
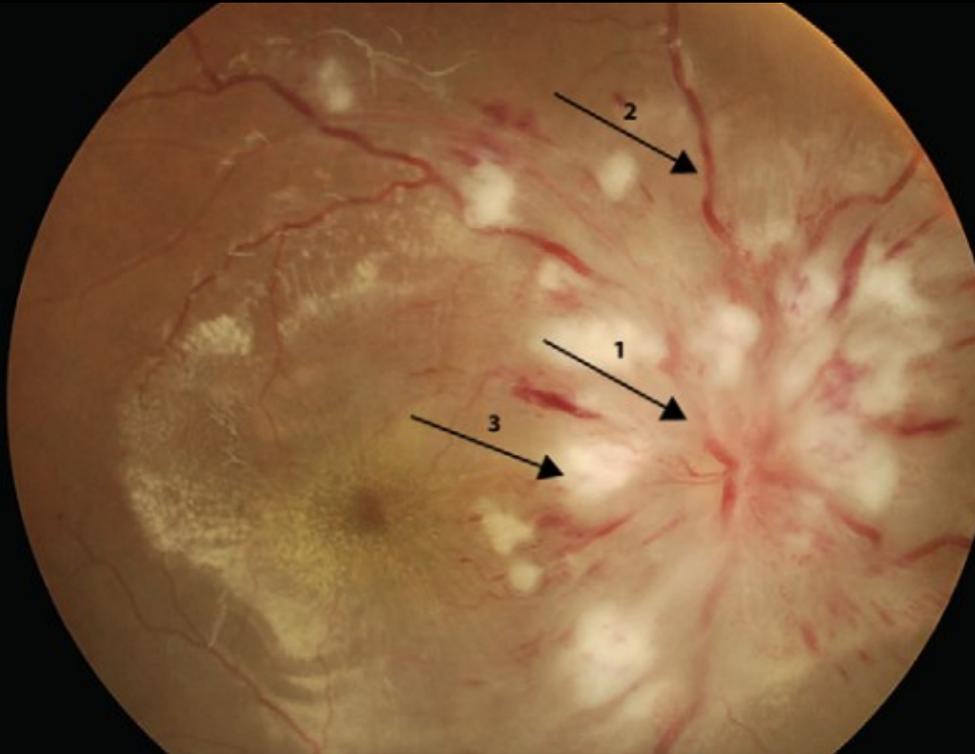


- **HTA = 1^{ère} cause de morbi-mortalité ajustée à l'âge**
 - 1,13 milliard d'individus en 2015
 - 1^{er} FDR de pathologie cardiaque ischémique, d'AVC, d'IRC et de démence
- En ophta :
 - Rétinopathie hypertensive
 - OAR/OVR
 - Macroanévrismes artériels
 - NOIANA
 - Aggrave la RD et la DMLA

L'œil est le seul organe permettant un accès à la microvascularisation de manière non invasive → fenêtre pour explorer l'état cérébral et la physiopathologie vasculaire



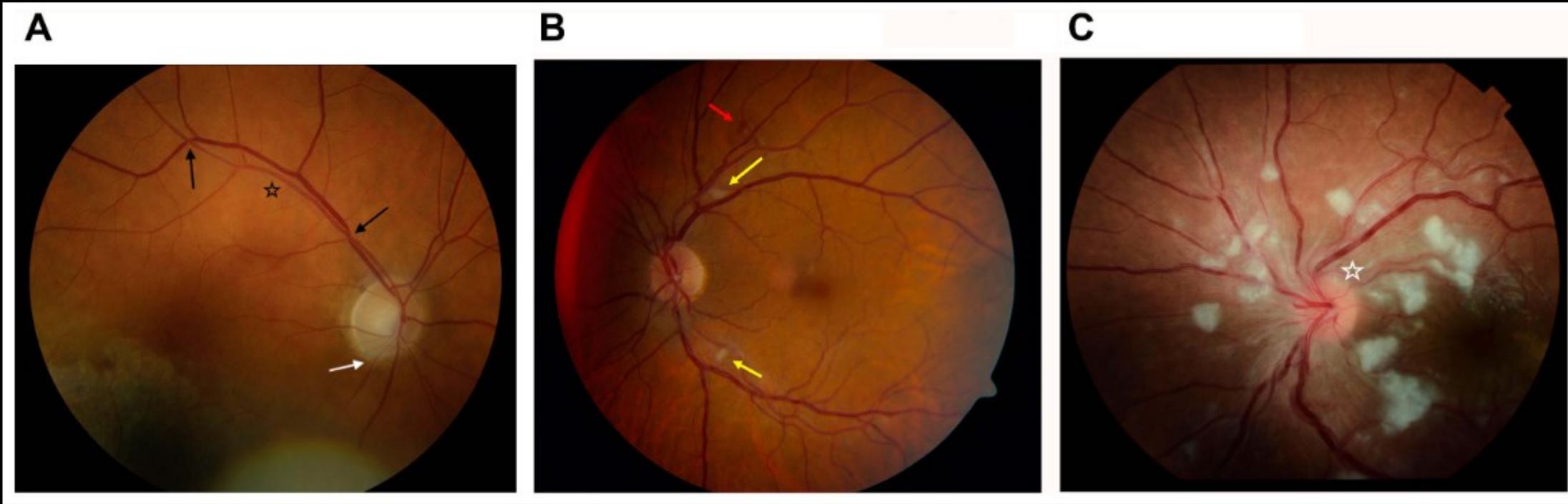
L'œdème papillaire: apanage des HTA aigues récentes



Rétinopathie hypertensive severe: nodules cotonneux, œdème papillaire, exsudats secs, occlusion artériolaire



Rétinopathie hypertensive



Minime

- Rétrécissement artériolaire diffus
- Croisement AV pathologiques

Modérée

- Rétrécissement artériolaire diffus
- Croisement AV pathologiques
- Nodules cotonneux
- Hémorragies

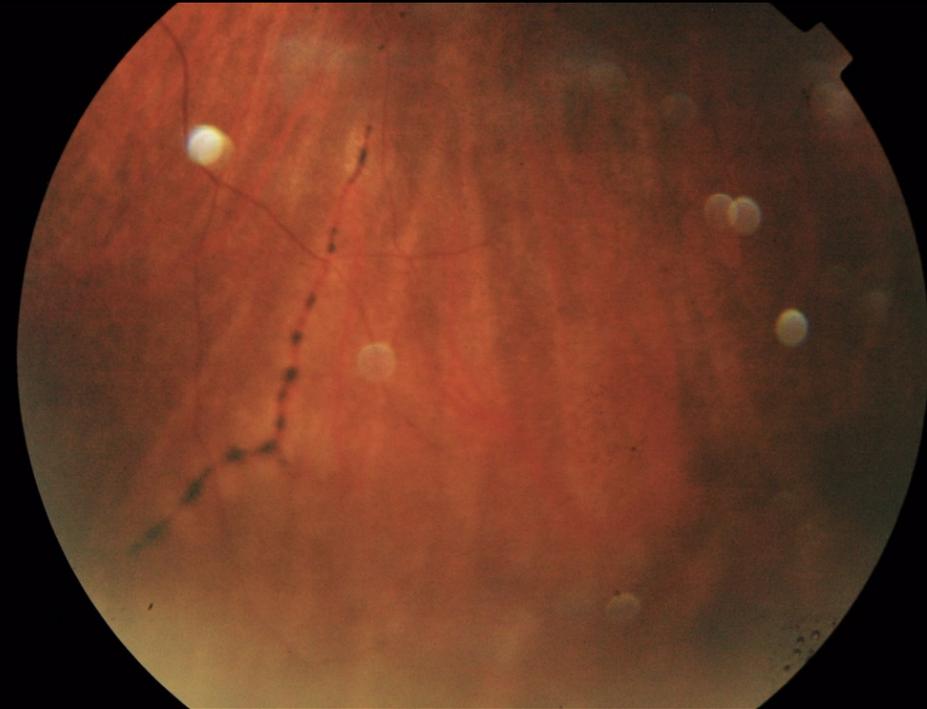
Sévère

- Rétrécissement artériolaire diffus
- Croisement AV pathologiques
- Nodules cotonneux
- Hémorragies
- Œdème papillaire

Signes plus accessoires: choréïdopathie hypertensive



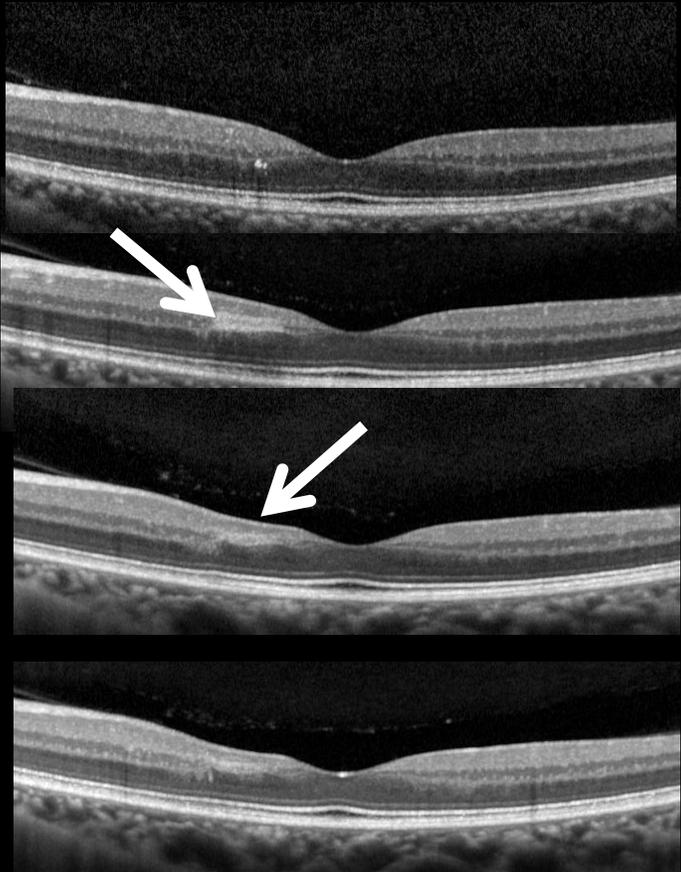
Taches d'Elschnig
= Ischémie de l'épithélium pigmentaire



Stries de Siegrist
= Taches d'Elschnig suivant une artère
choroïdienne

2019, *Acute Hypertensive Retinochoroidopathy Secondary to an Anti-cancer Drug (apatinib) : The First Case Report*,
Bangtao et al. *Front Med (Lausanne)*

2021, *Siegrist streaks in malignant hypertension*, Gratiot et al. *Journal Français d'Ophtalmologie*



03/19

04/19

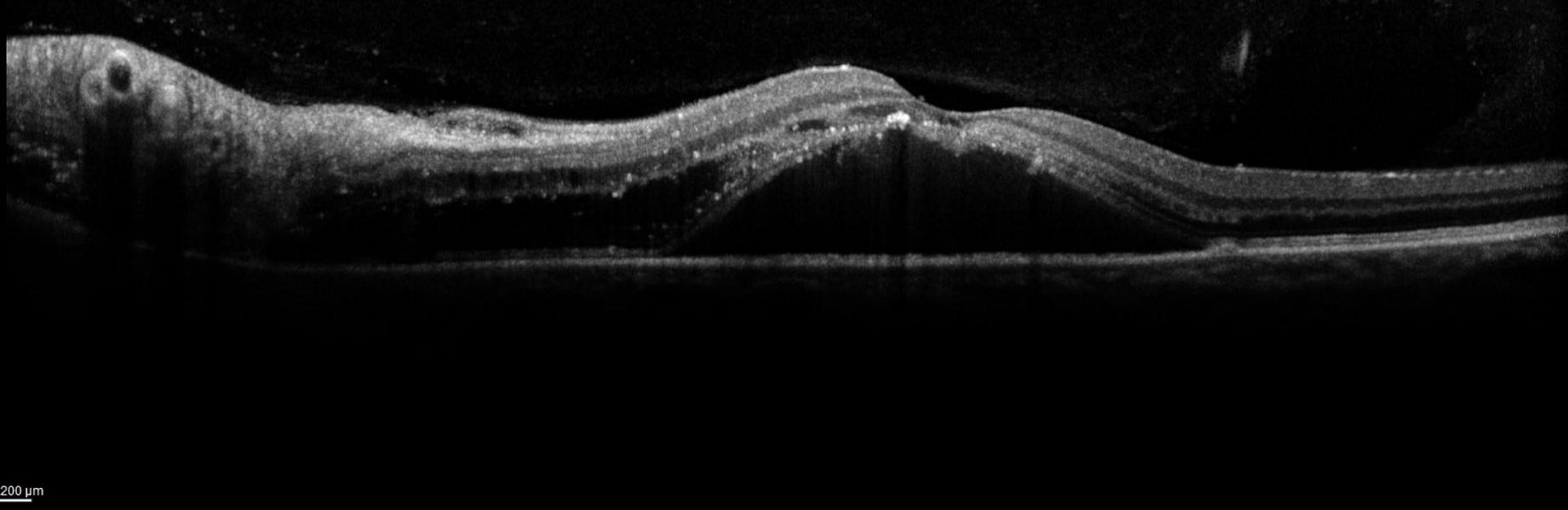
05/19

07/19



Lésion hyperréfléctive des couches internes de la rétine traduisant une ischémie rétinienne focale

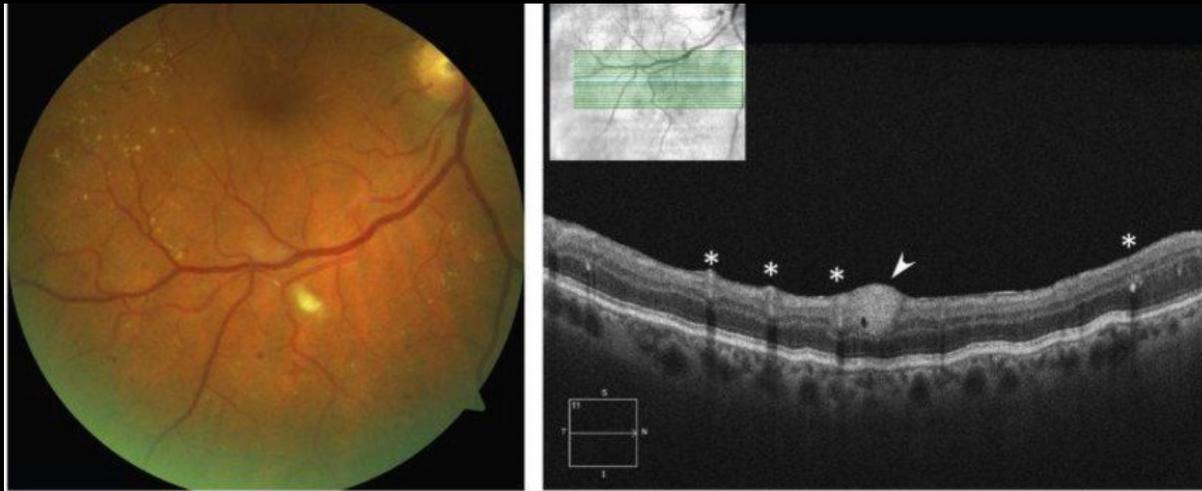
OCT des HTA malignes



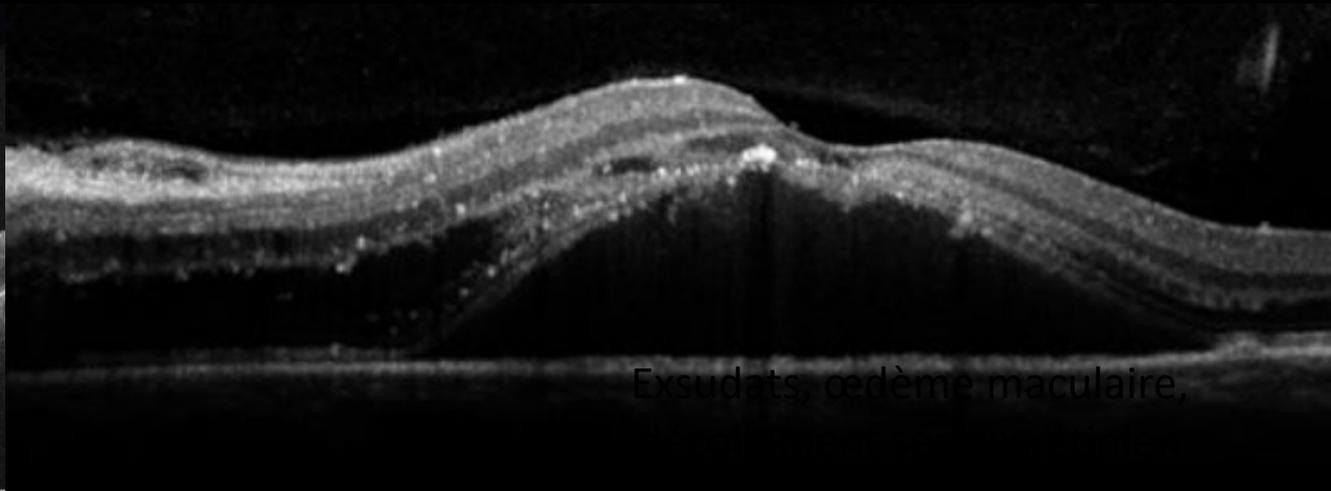
08/04/2011, OS
IR&OCT 30° ART [HR] ART(19) Q: 36

Décollement séreux rétinien

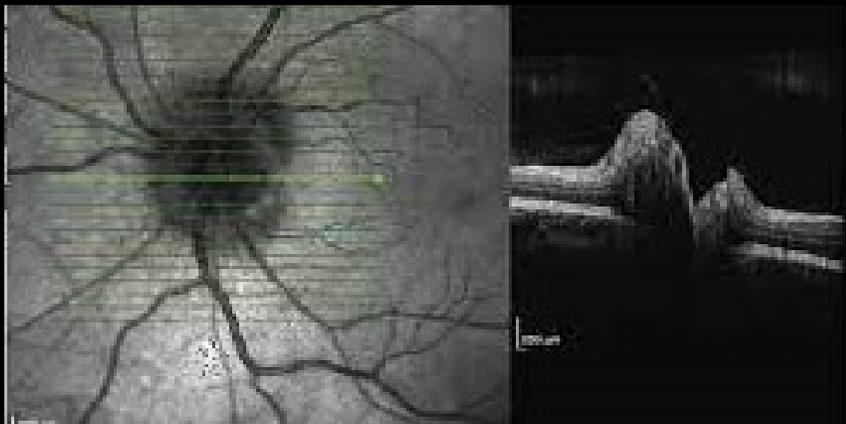
Nouveaux signes de la rétinopathie hypertensive aiguë: tomographie de cohérence optique (OCT)



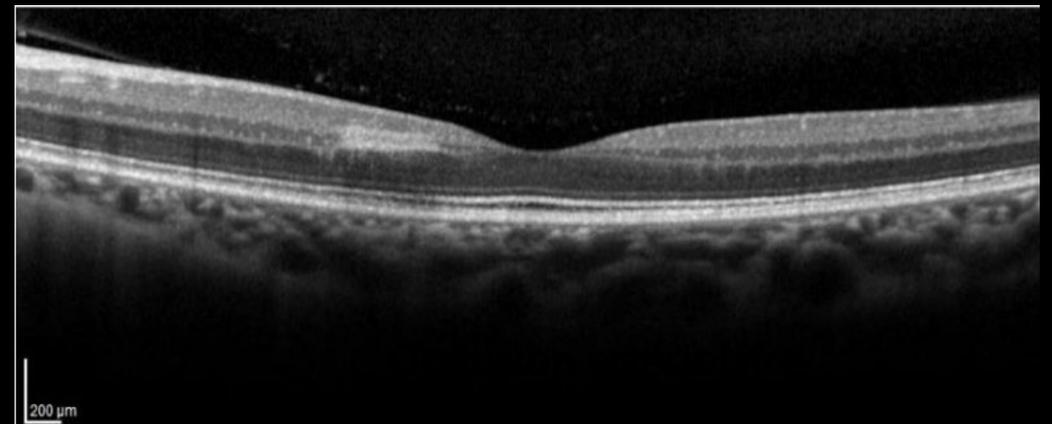
Nodule cotonneux



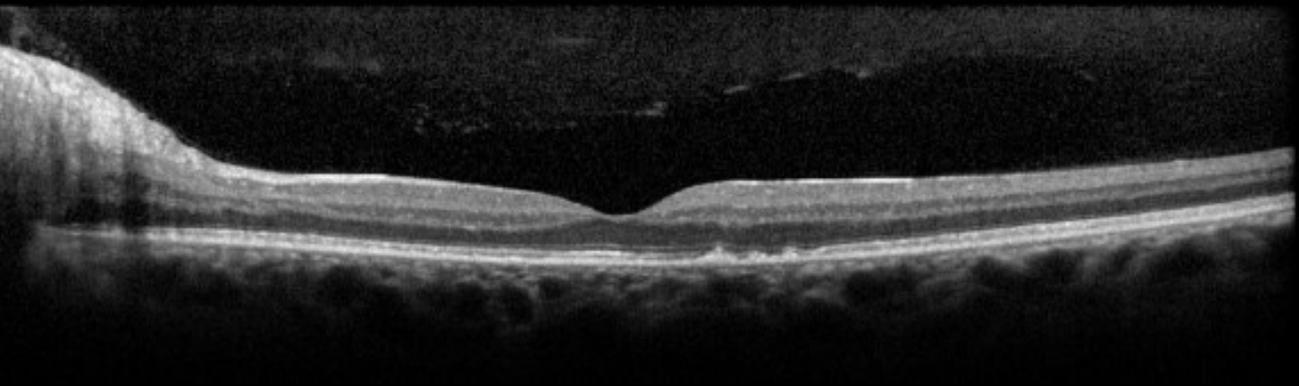
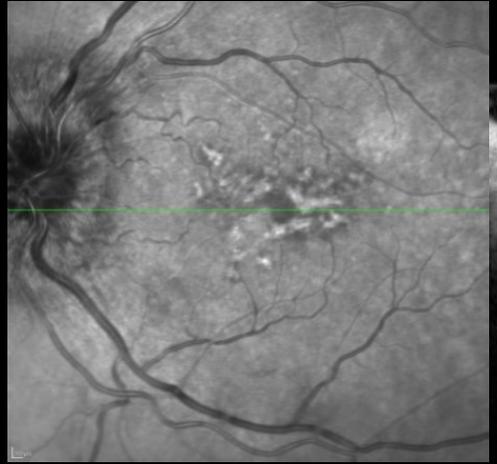
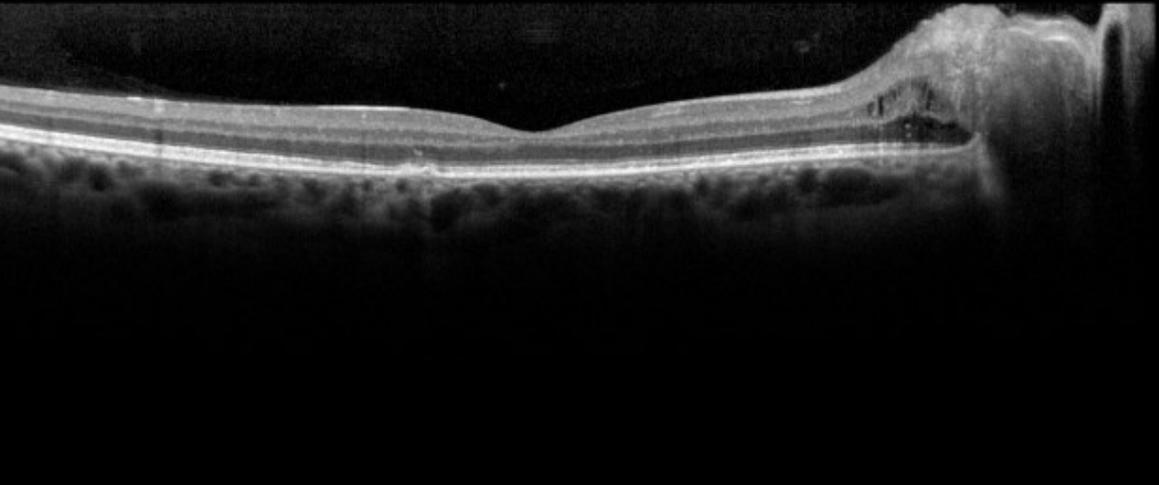
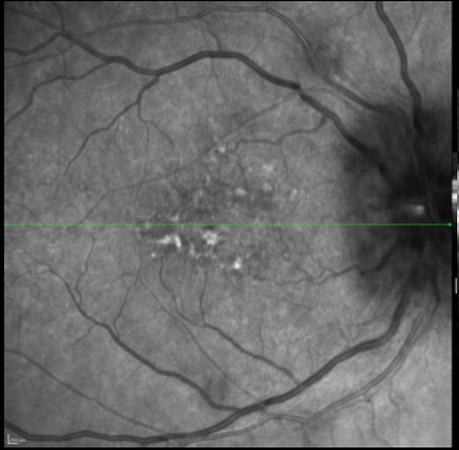
Exsudats, œdème maculaire,



Œdème papillaire



Séquelles d'HTA aigue



HTA maligne et OCT-A

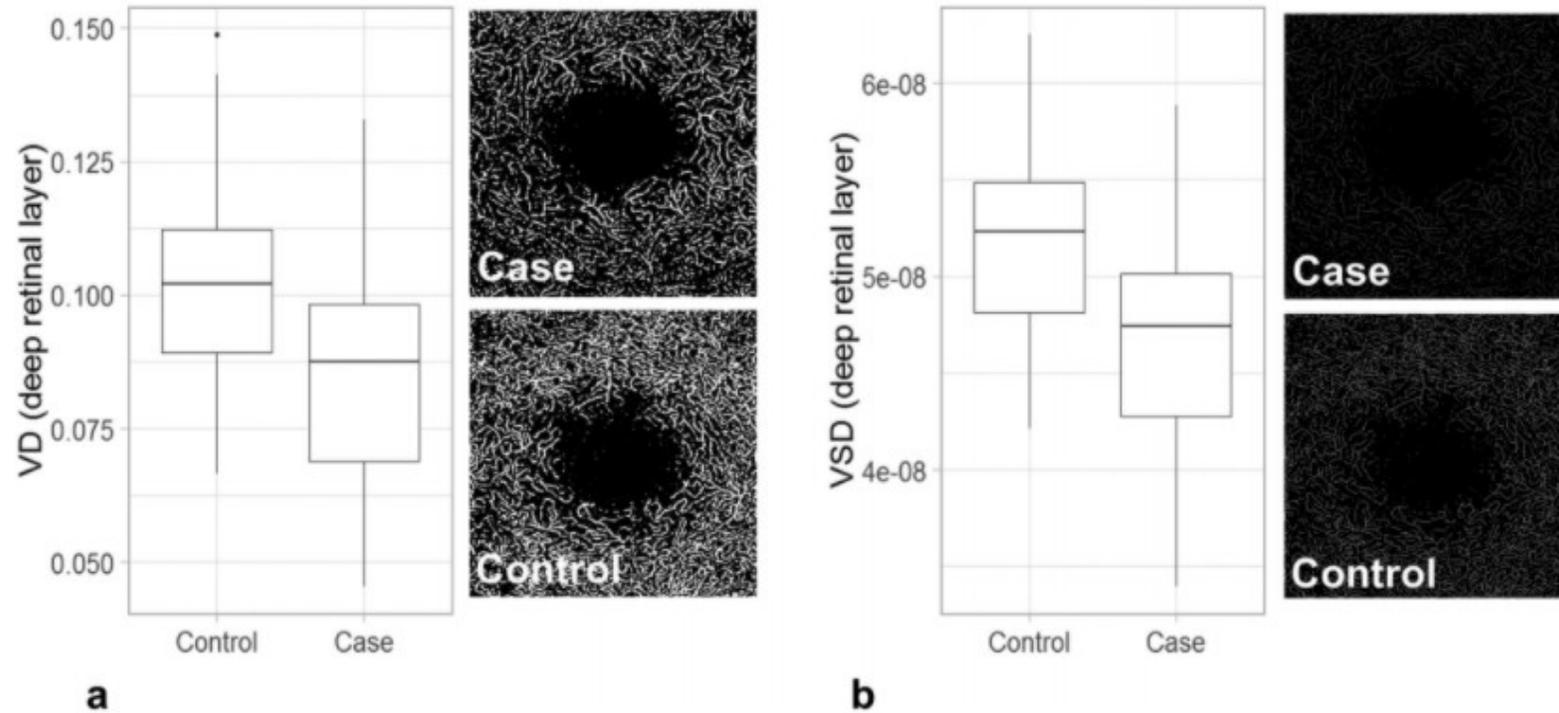
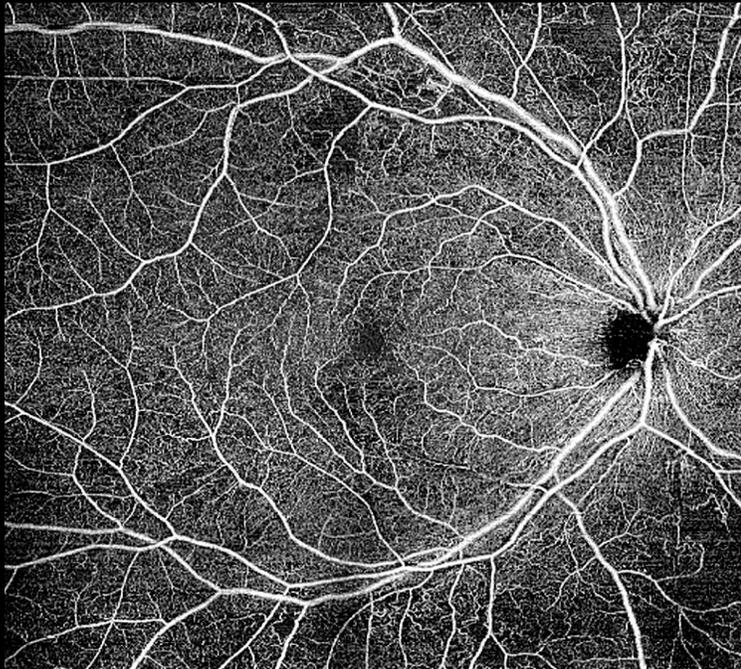
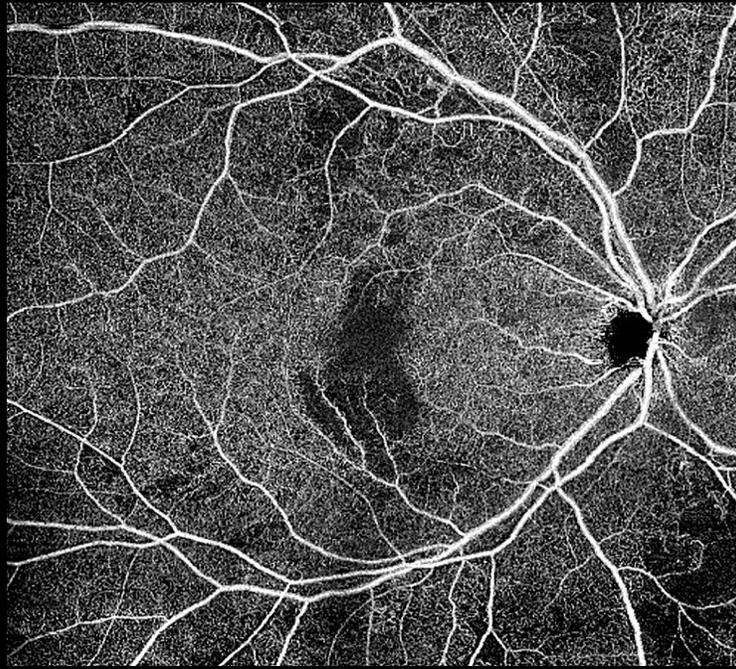


Figure 1. Vessel density (a) and vessel skeleton density (b) values of the deep retinal layer in subjects with hypertensive crisis and controls with examples of binarized (a) and skeletonized (b) OCTA images. Values more than 1.5 times the interquartile range from the quartiles were considered outliers according to Tukey's rule.³¹

OCT Angiographie: non-perfusion focale de la DVP



Plexus capillaire superficiel

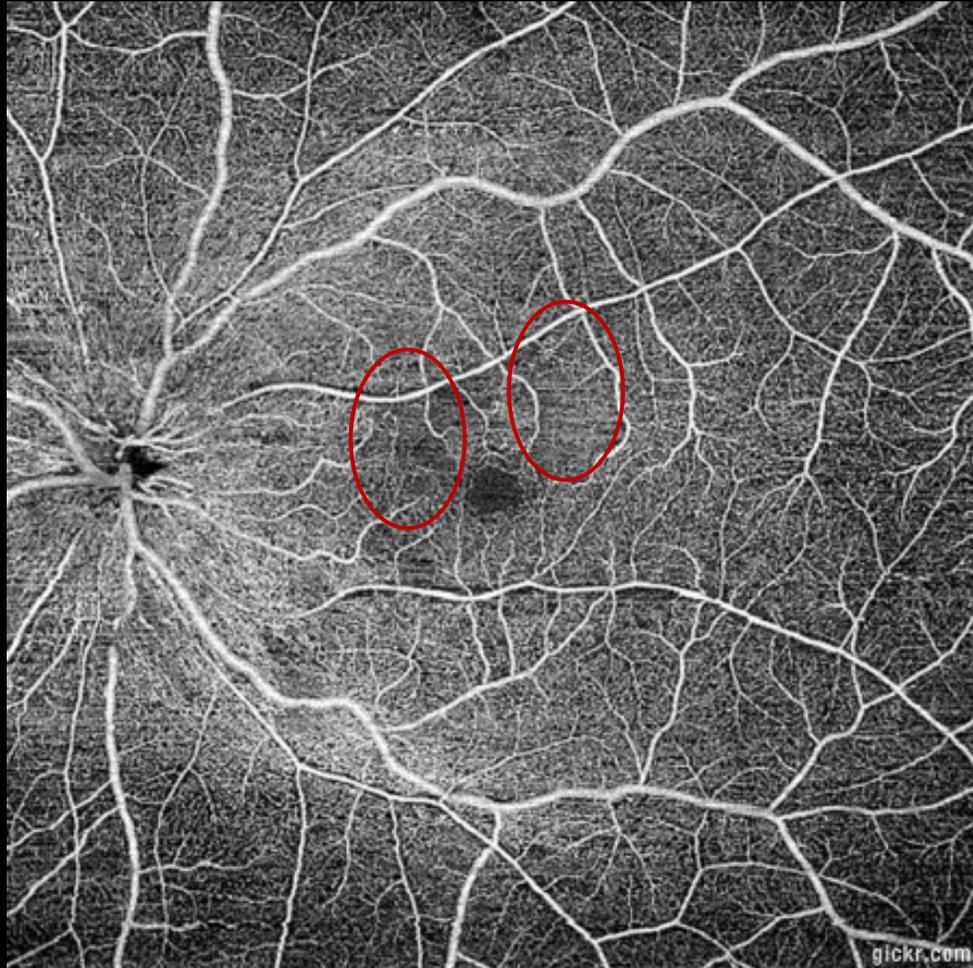


Plexus capillaire profond

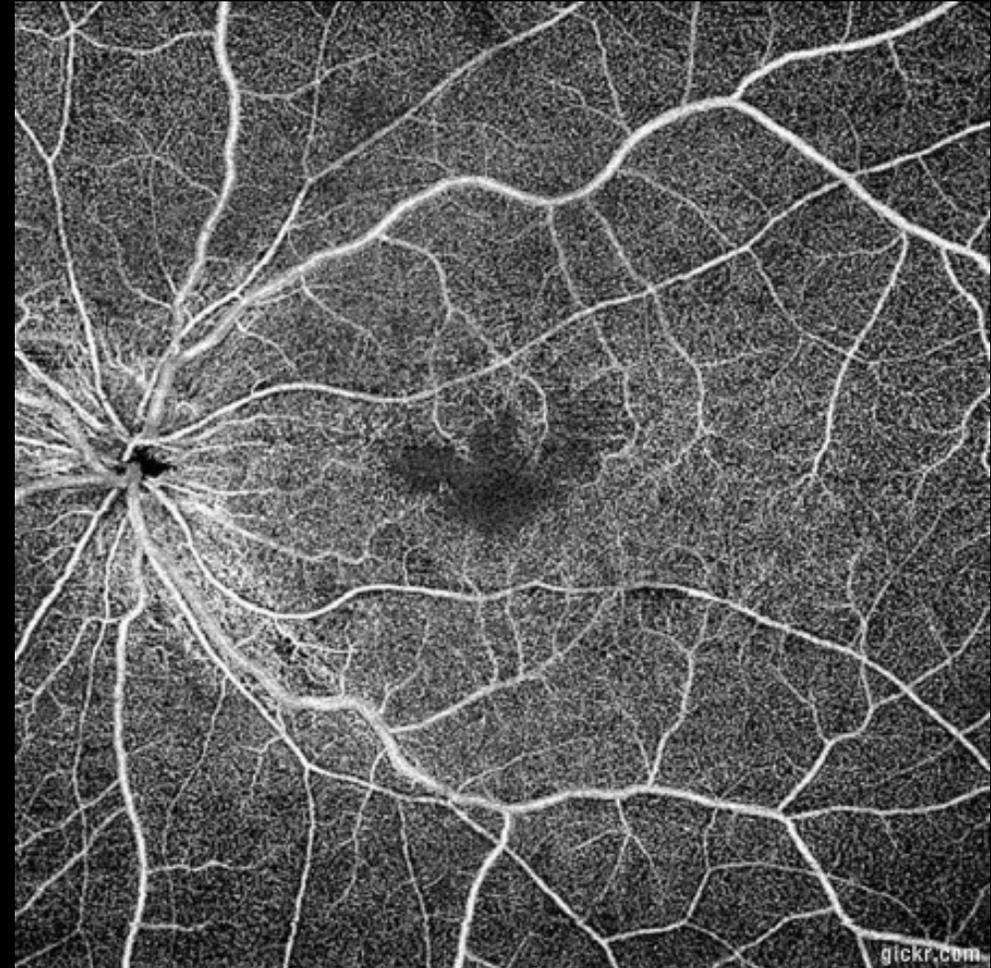


*Choriocapillaire : pas
d'anomalie de perfusion*

OCT – Angiographie: nonperfusion focales

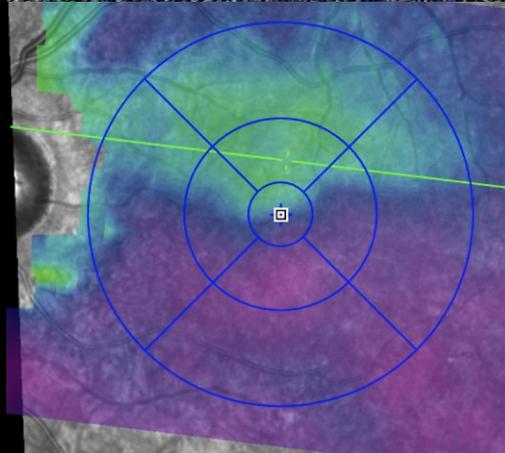
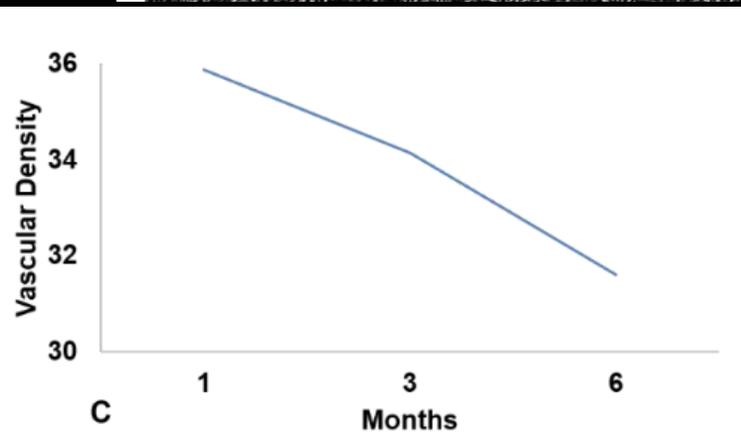
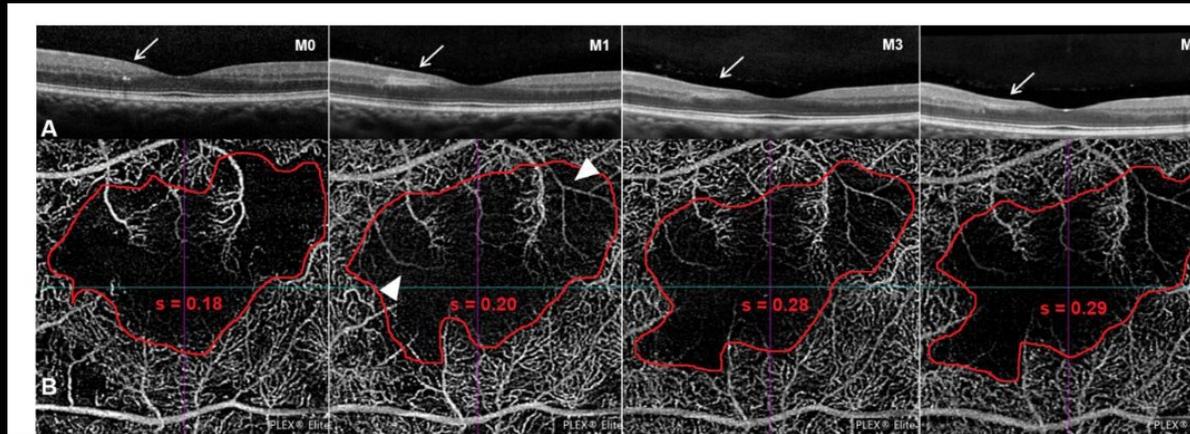


Plexus capillaire superficiel : obstruction de deux artérioles puis reperfusion

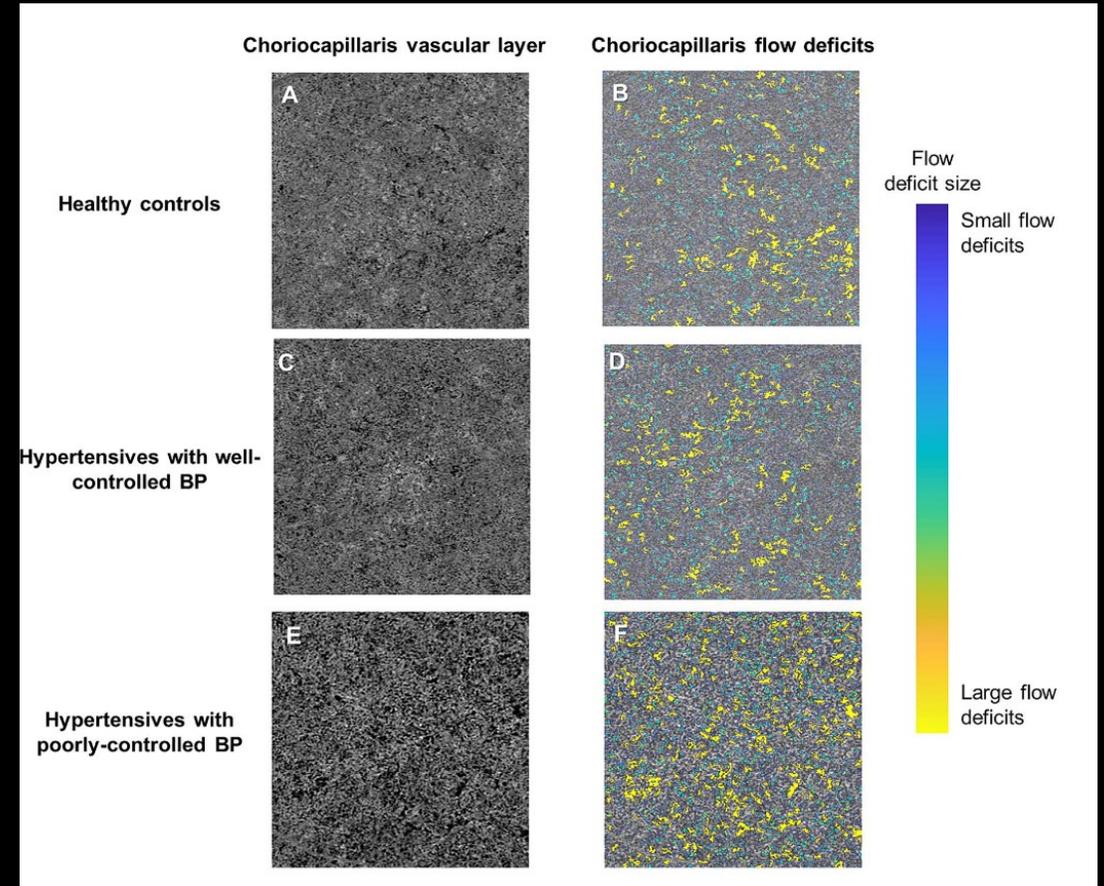


Plexus capillaire profond : hypoperfusion secondaire

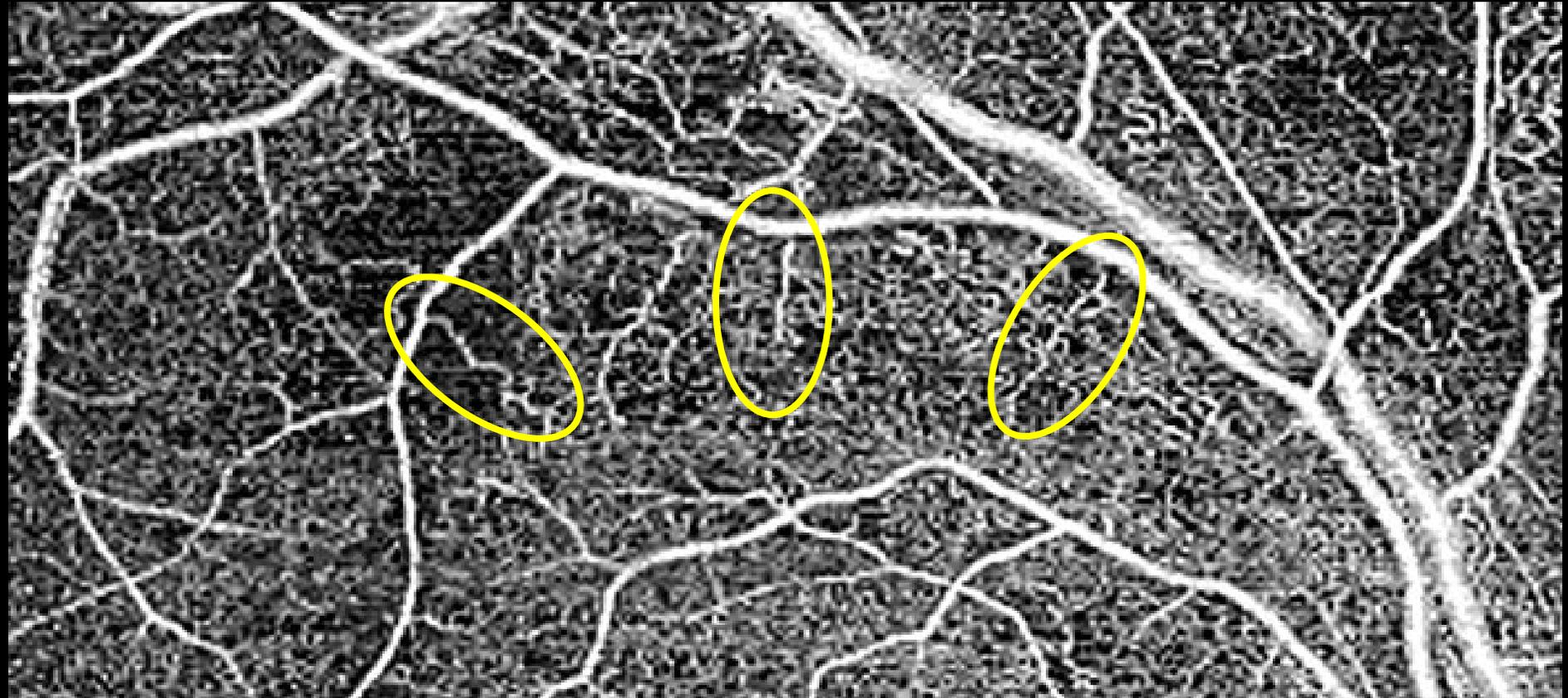
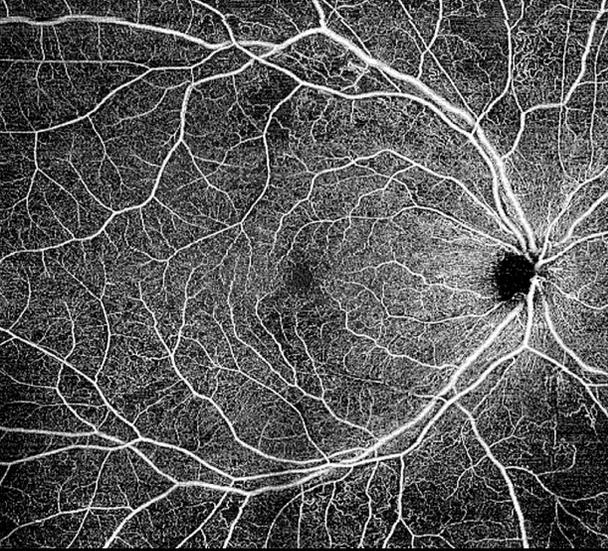
OCT-Angiographie

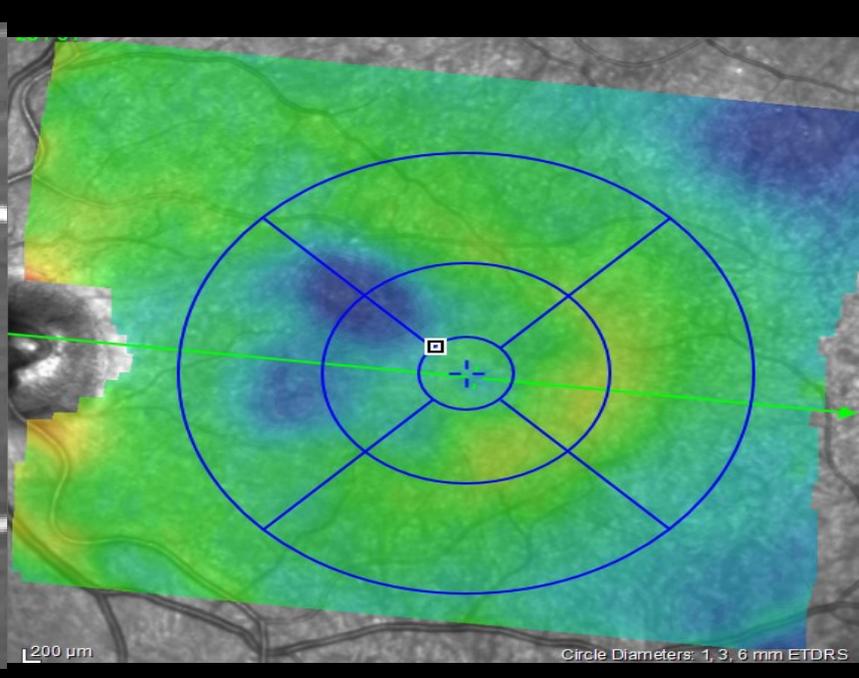
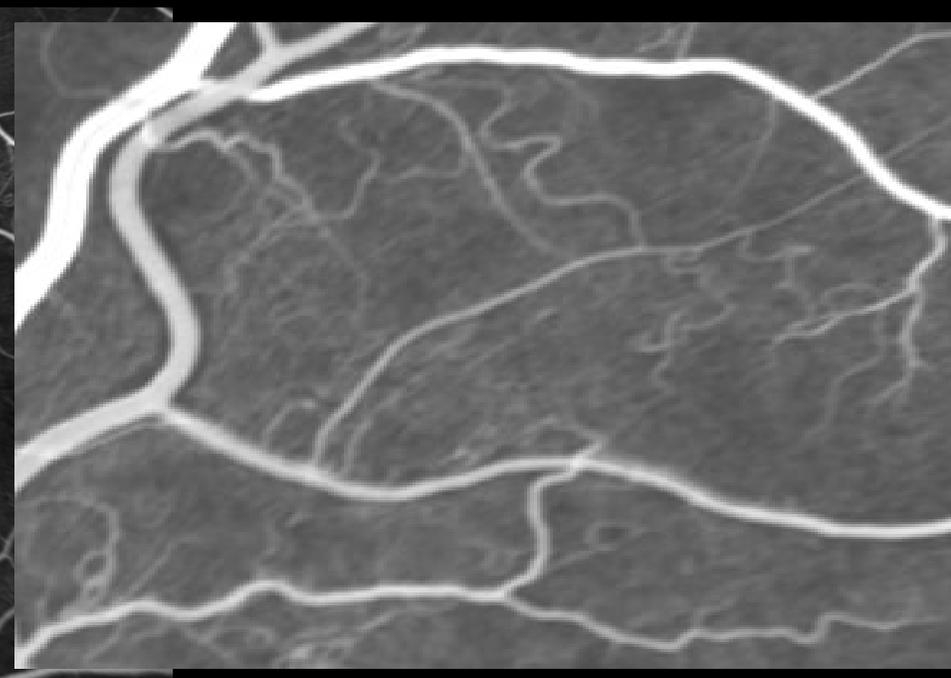
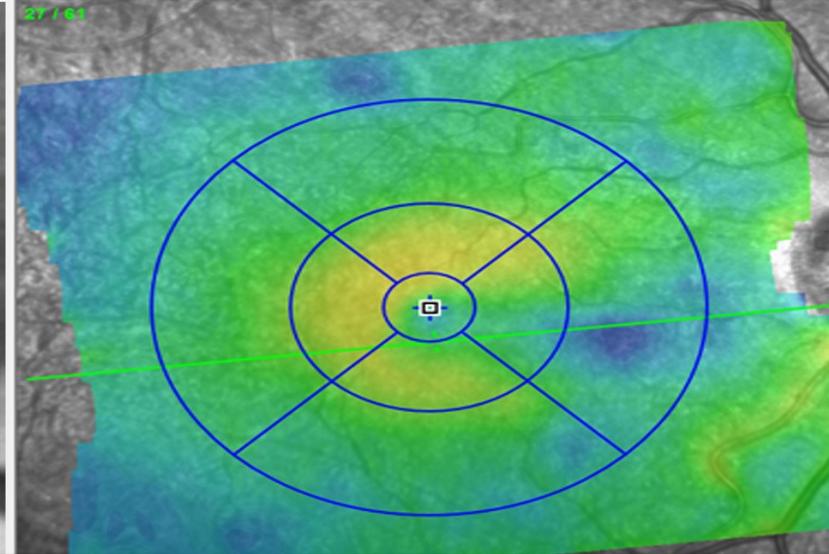
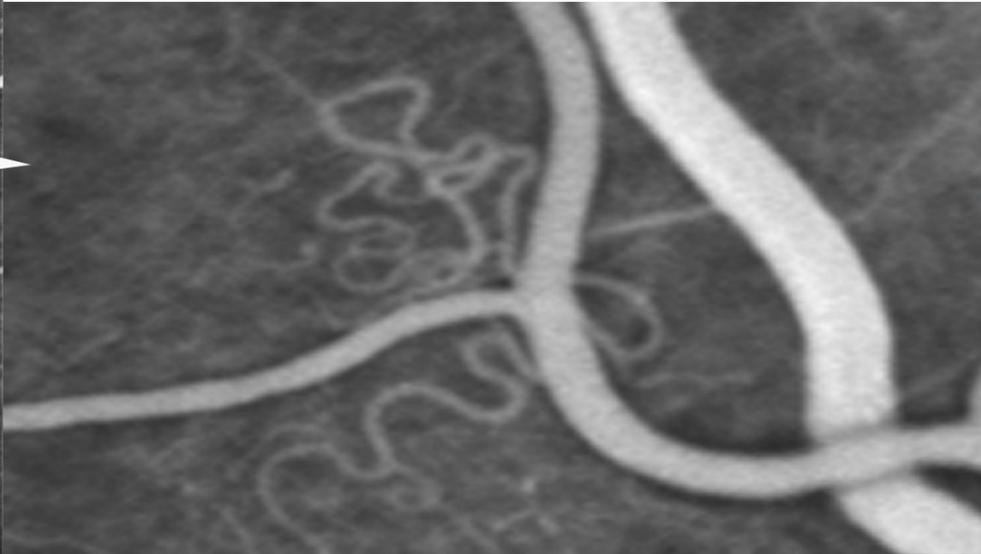


Diminution de la perfusion de capillaire rétinienne (1)



Diminution de la perfusion de la choriocapillaire? (2)



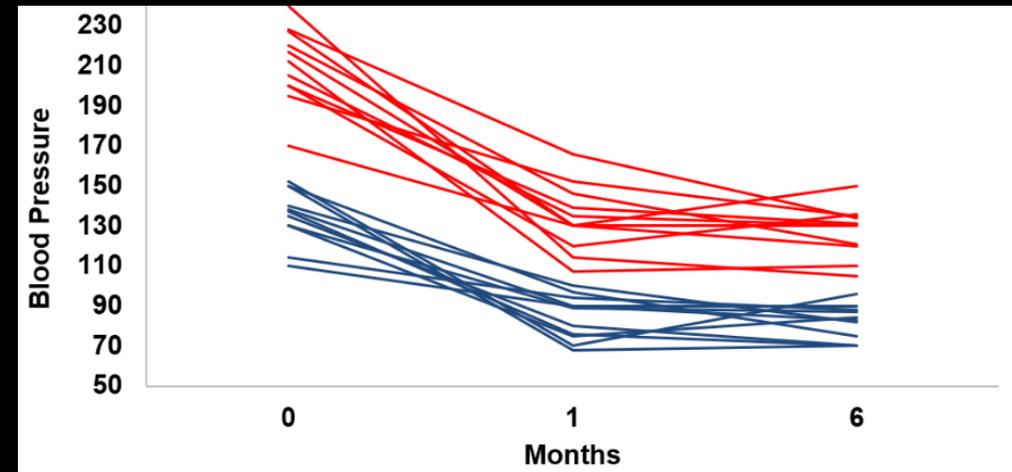


Vasomotricité rétinienne au cours HTA maligne

- Suivi à plus long terme de patients HTA maligne
- **Evaluation qualitative = recherche d'anomalies focales**
 - Tortuosité vasculaire
 - Recherche de sténoses/vasolidations focales
 - Pertes capillaires focales
- **Evaluation quantitative = étude des processus diffus**
 - Mesure des paramètres vasculaires (WLR...)
- Sélection des patients HTA maligne sur > 6 mois
- Montages et alignements des images en AO-FIO (rtx1)
- Mesures des paramètres vasculaires sur une zone prédéfinie (« zone de référence »)
- Recherche de variations focales
- Mapping OCT Spectralis et OCT-A Plexe-Elite

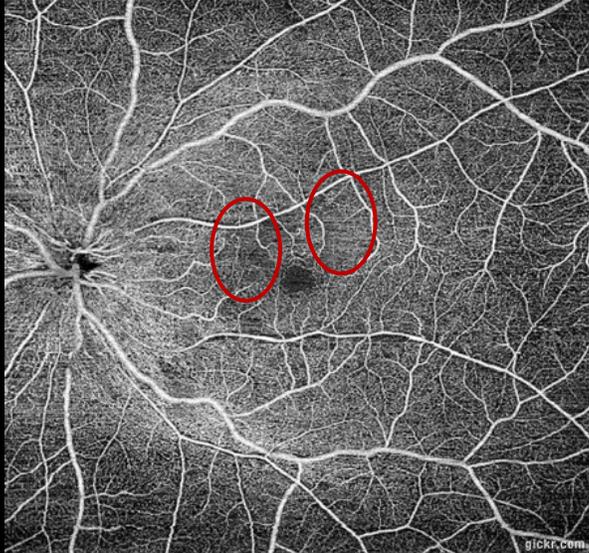
Population étudiée

- 16 patients
- 81% Hommes
- 43 ans [29-65 ans]
- Suivi 12,1 mois [3-26]
- OCT, OCTA et OOA

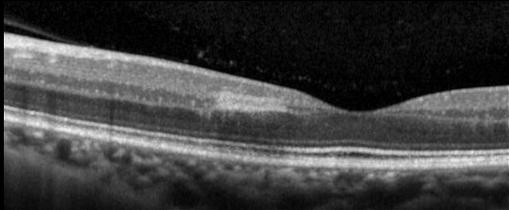
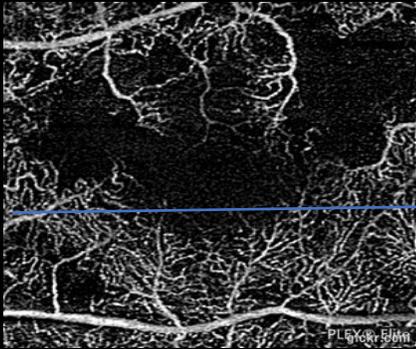
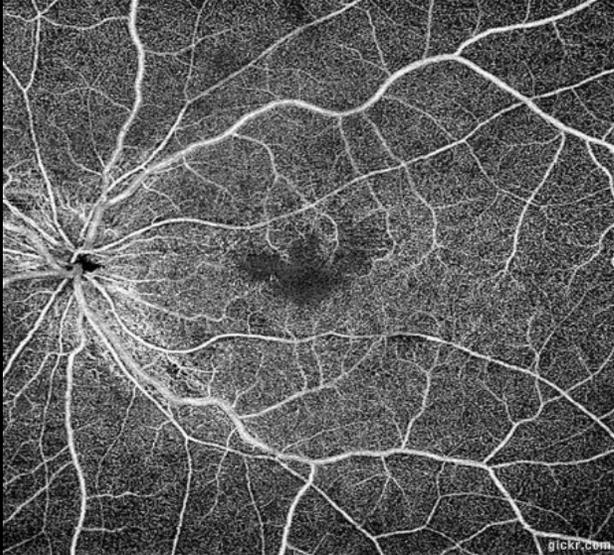


Occlusions d'artérioles secondaires pérимaculaires

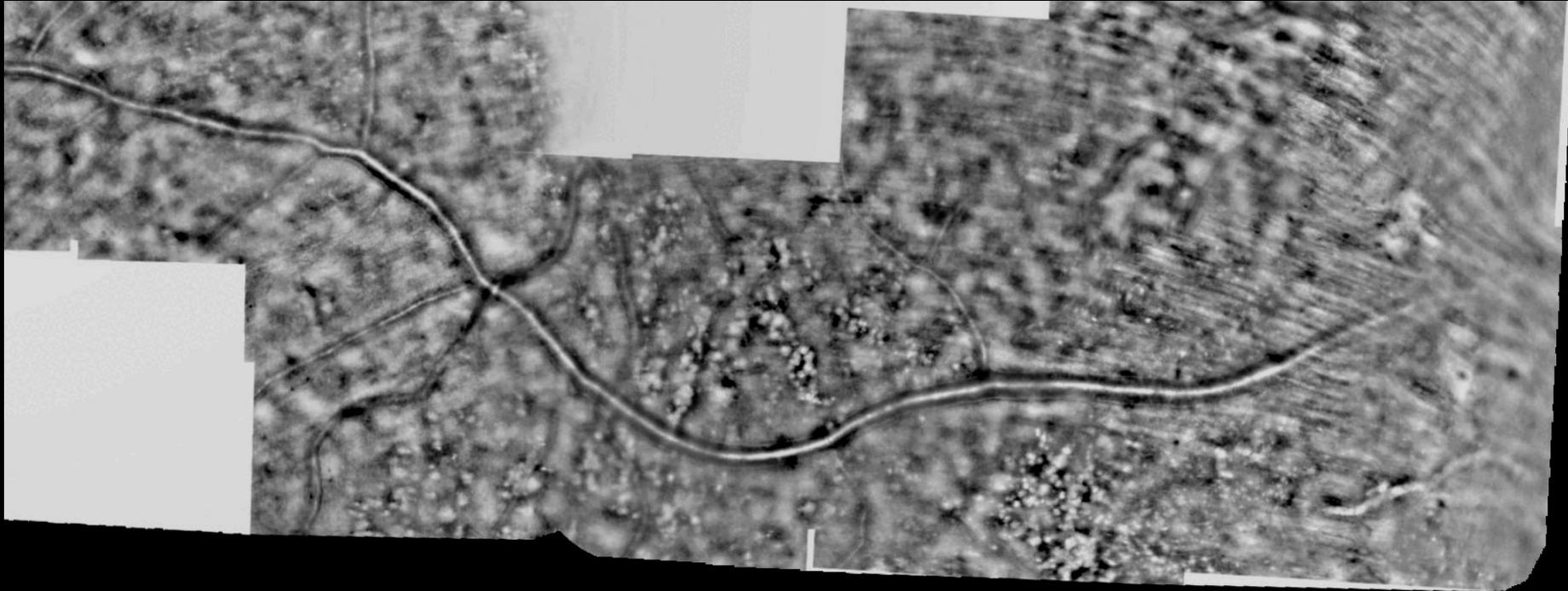
Plexus capillaire superficiel : obstruction de deux artérioles puis reperfusion



Plexus capillaire profond : hypoperfusion secondaire

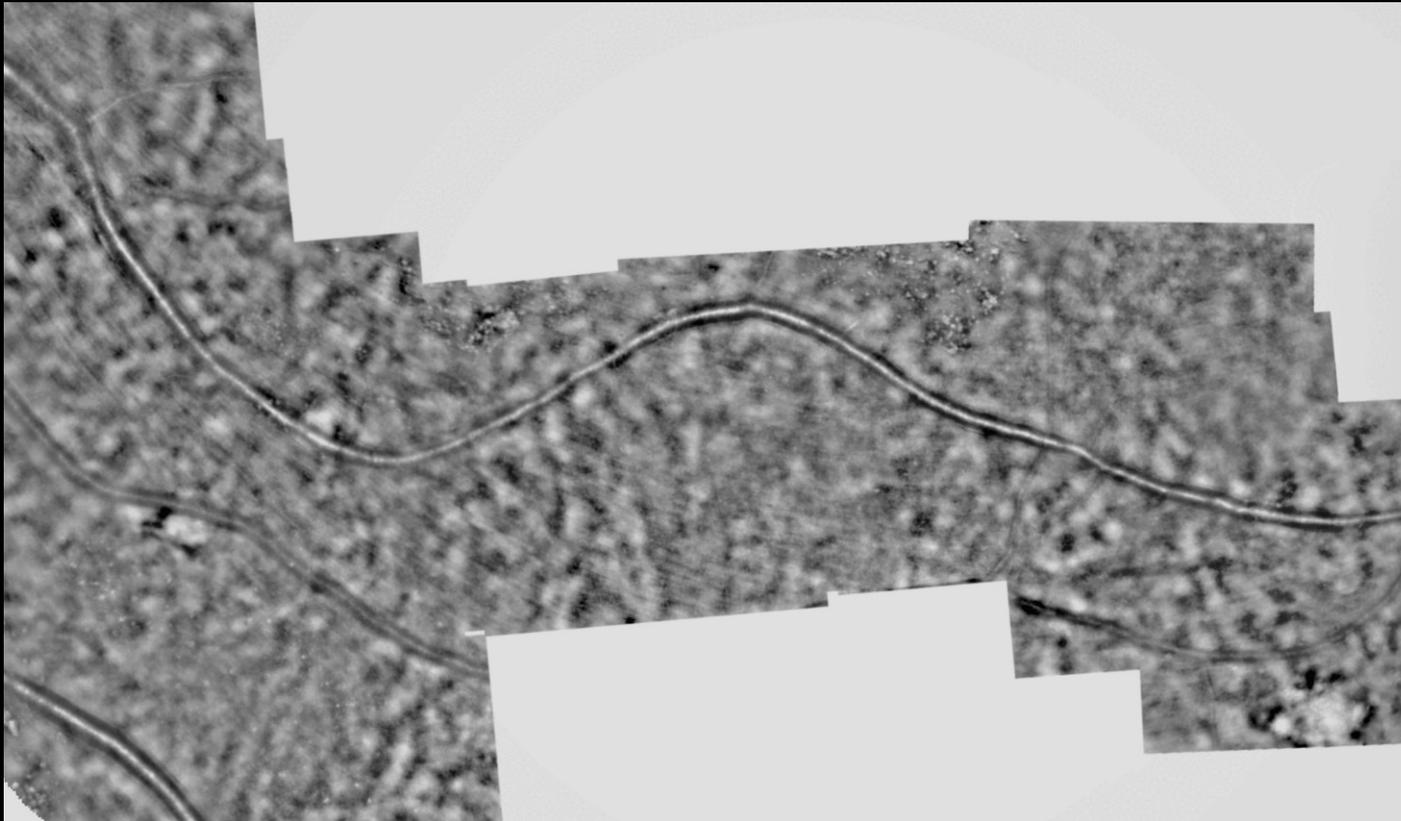


Time-lapse sur 2 ans après épisode d'HTA maligne



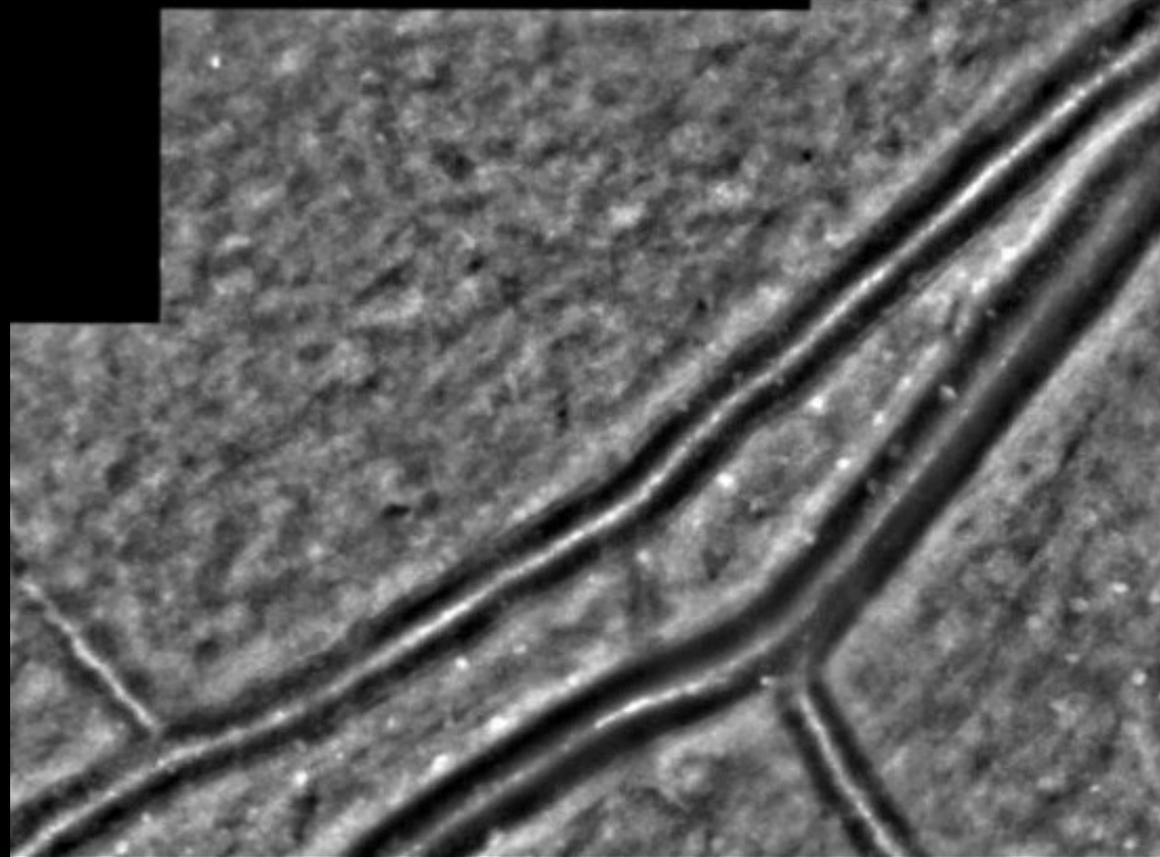
26 mois

Etude de la tortuosité artérielle post-critique



12 mois

Vasoconstriction focale post-critique

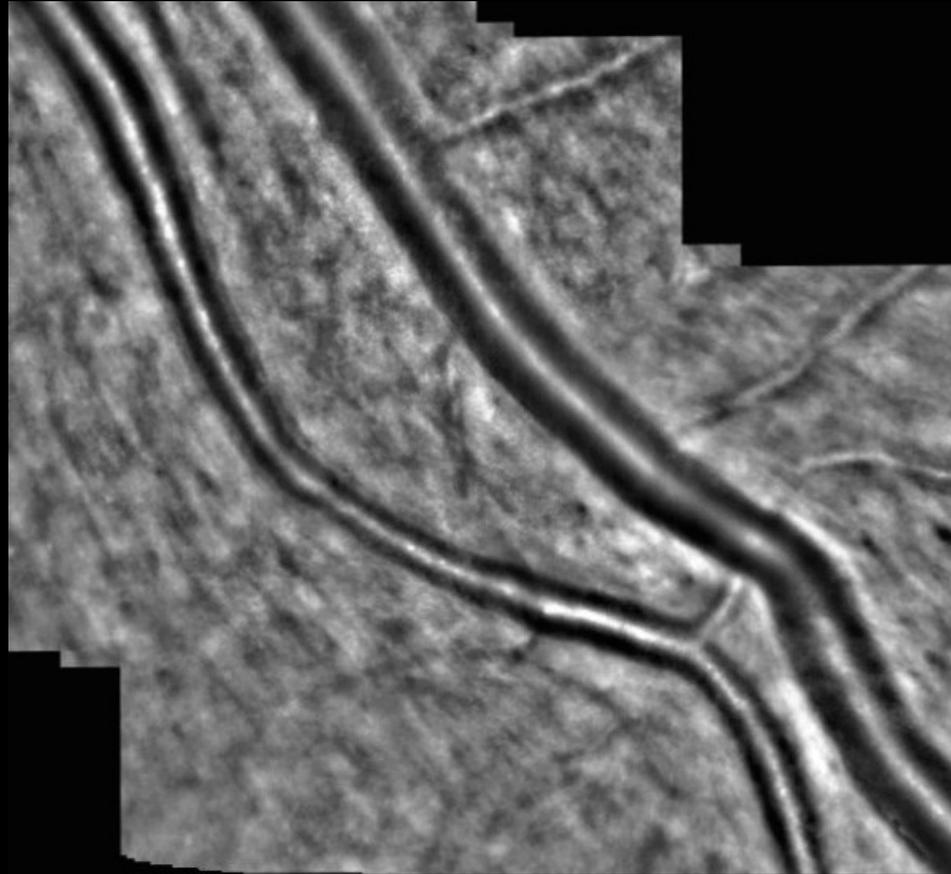


19% des patients



6 mois

Vasodilatation focale post-critique

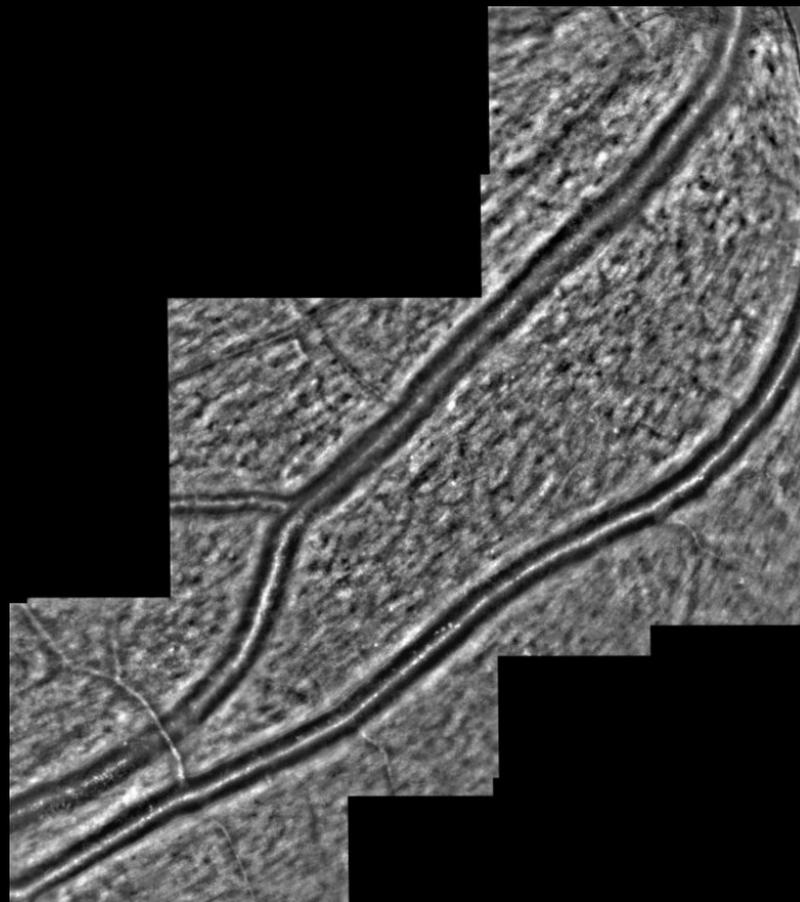


13% des patients



17 mois

Sténose diffuse

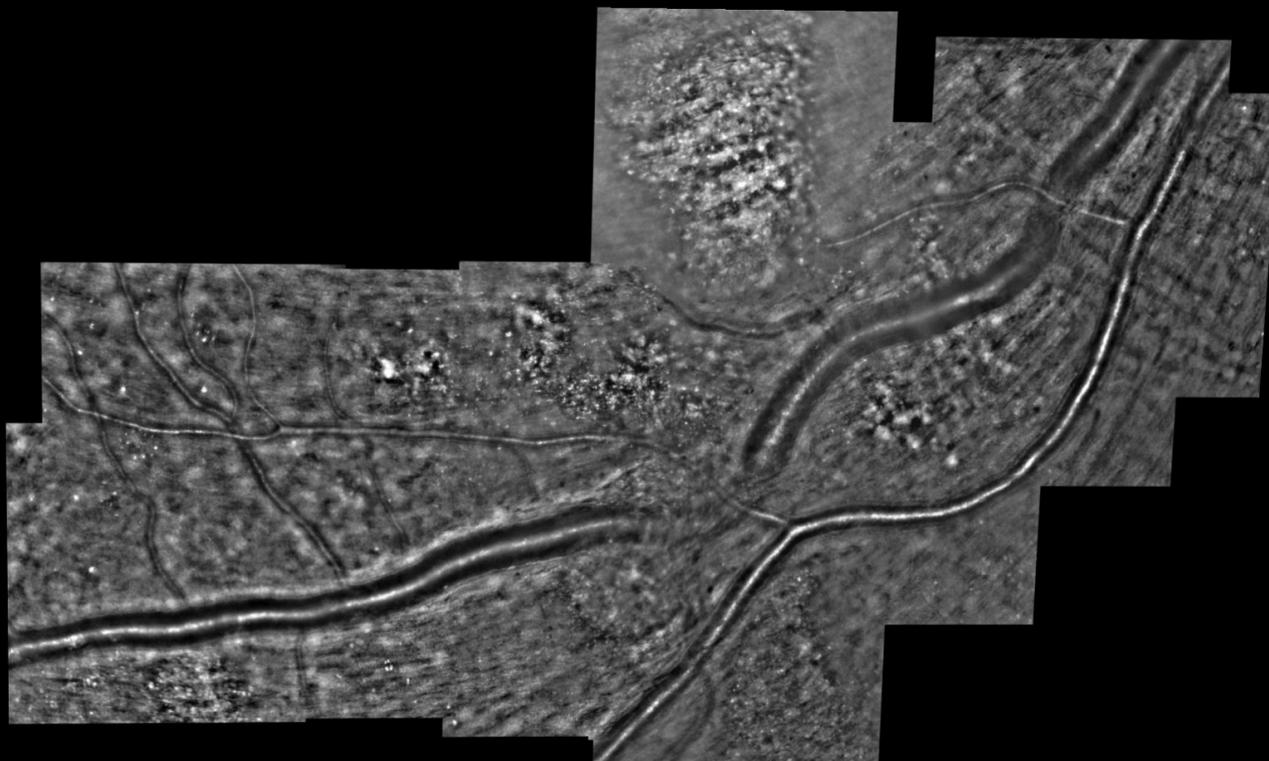


25% des patients



13 mois

Vasodilatation diffuse



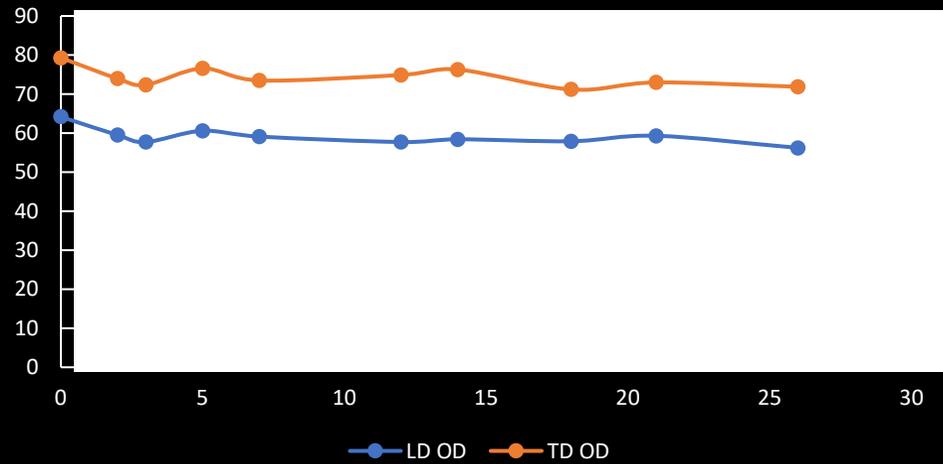
25% des patients



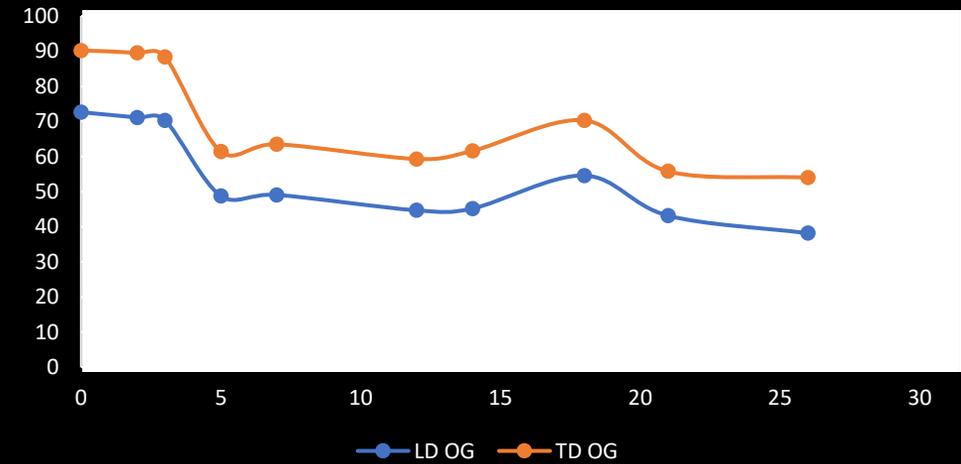
10 mois

Suivi des paramètres vasculaires

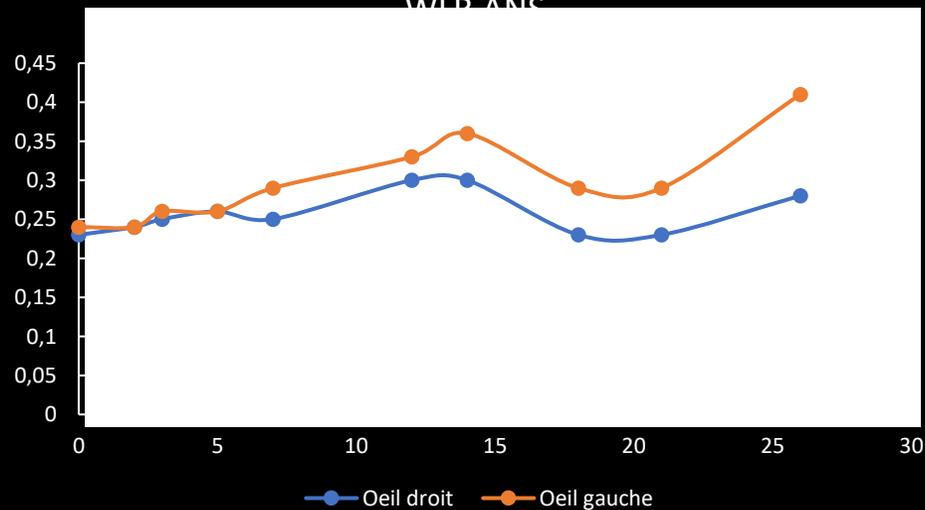
Diamètres Oeil droit ANS



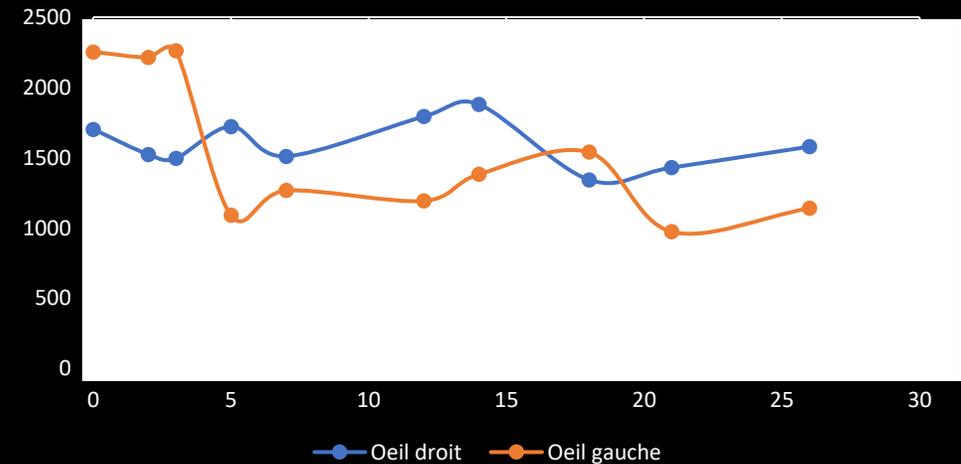
Diamètres OG ANS



WLD ANS

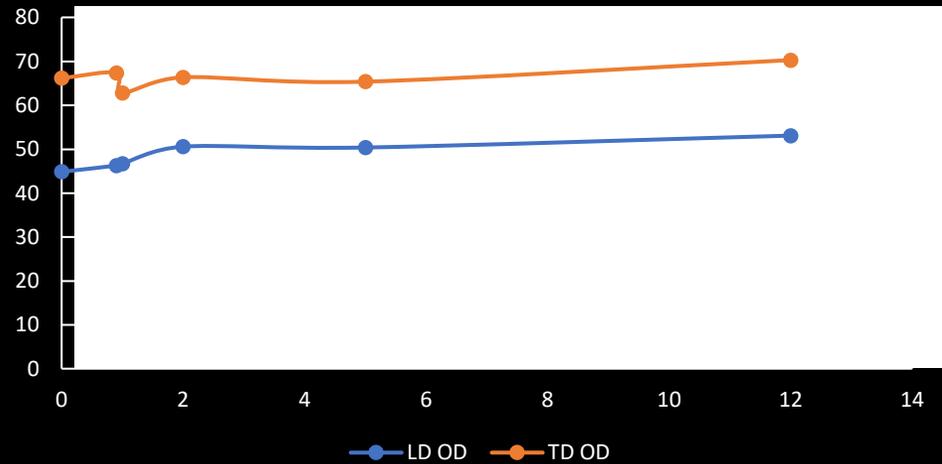


WCSA ANS

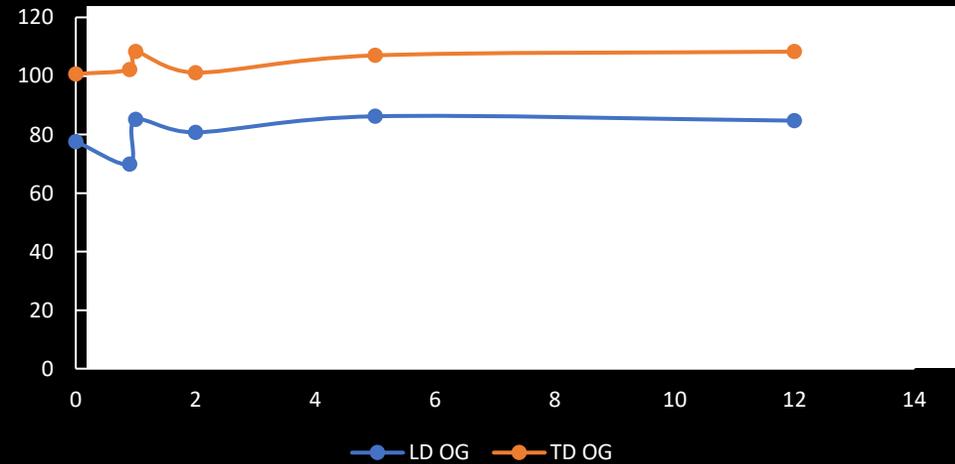


Suivi des paramètres vasculaires

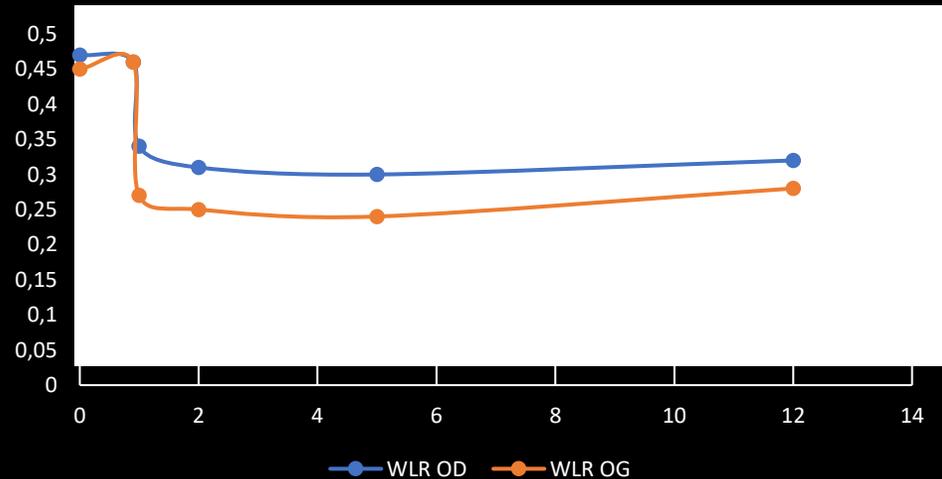
Diamètres Oeil droit INJ



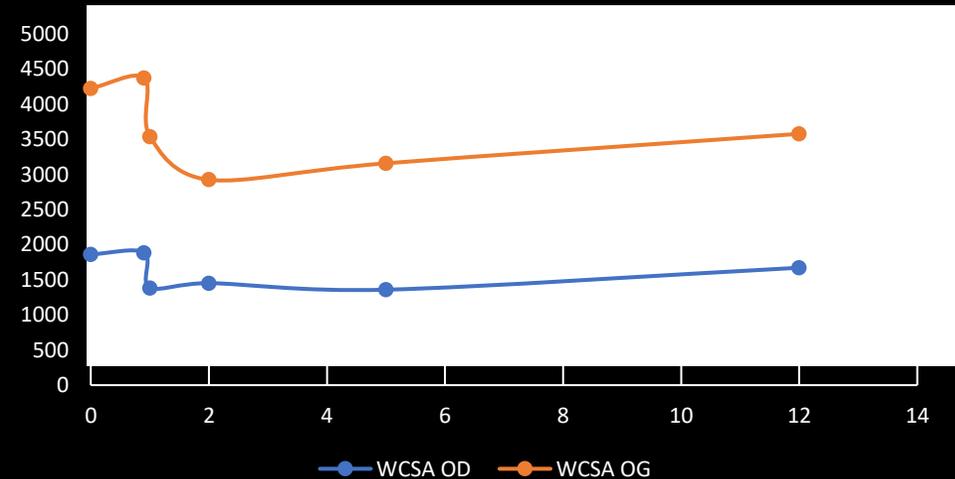
Diamètres Oeil gauche INJ



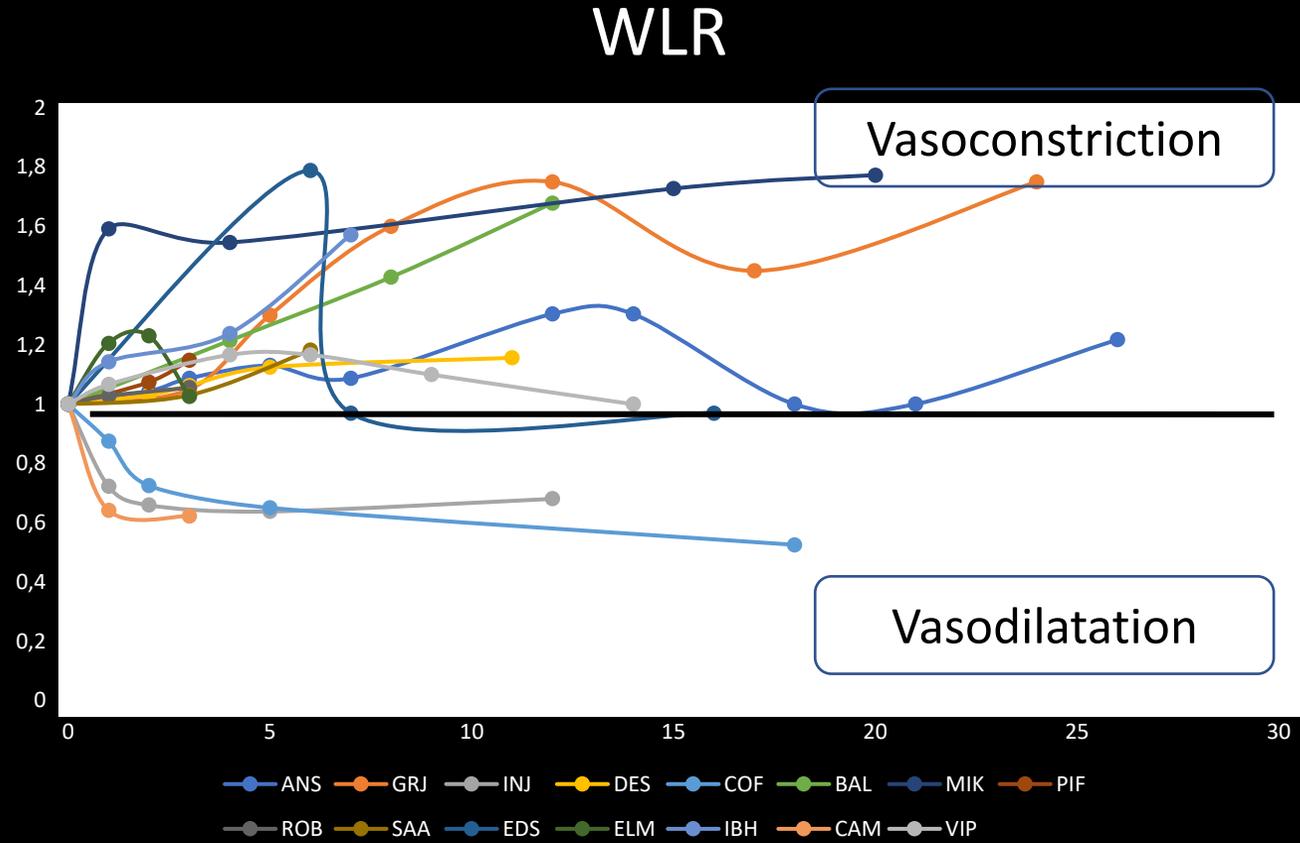
WLR INJ



WCSA INJ



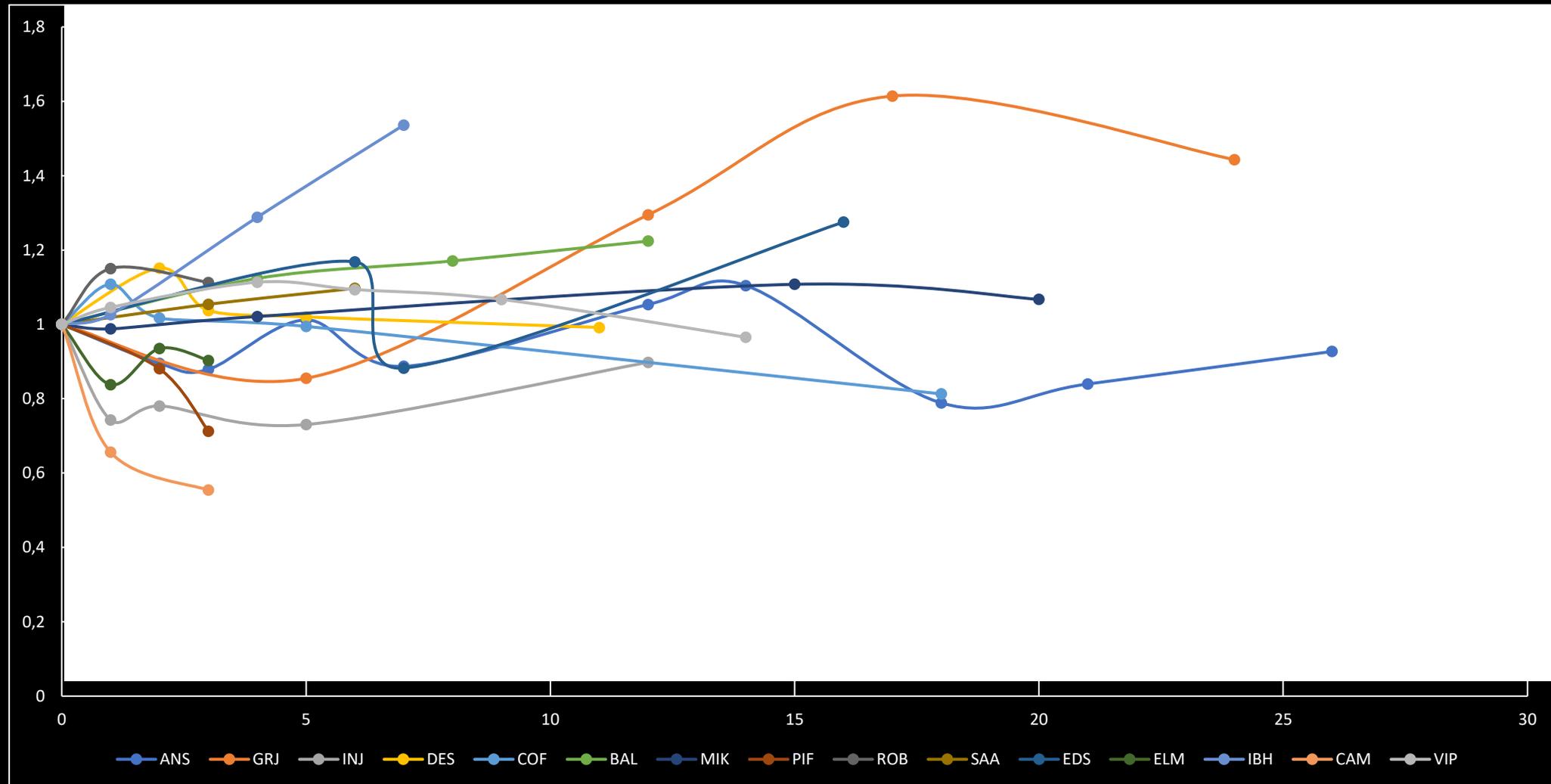
Evolution du WLR



Données brutes

Normalisé au premier examen

Evolution du WCSA (normalisé au premier examen)

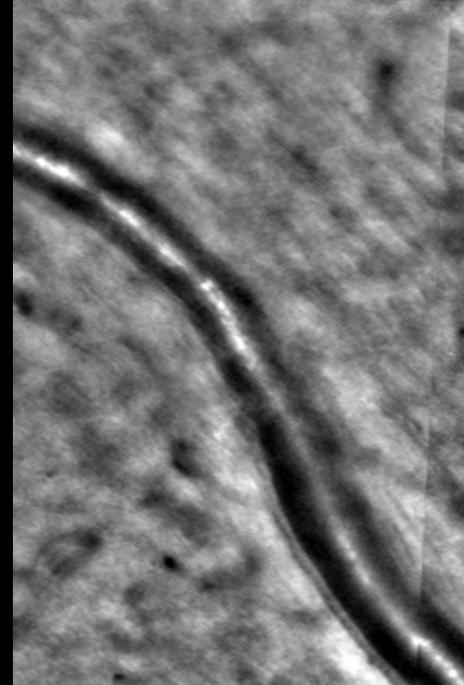
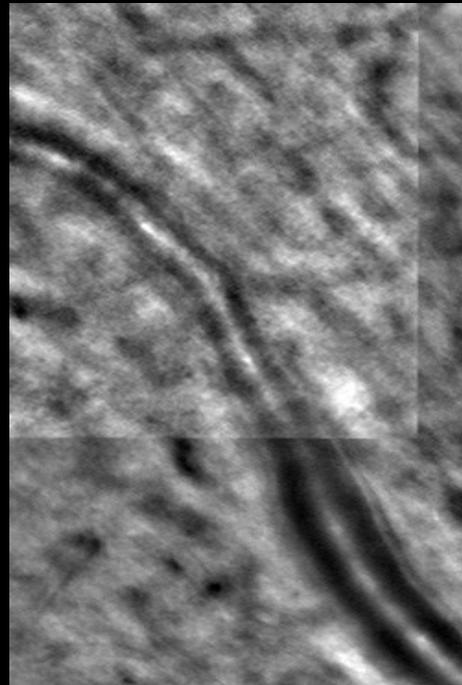
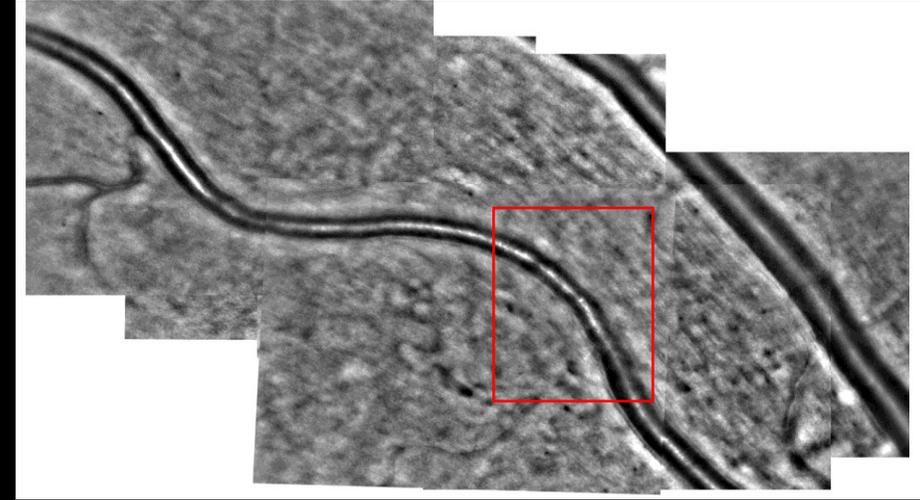
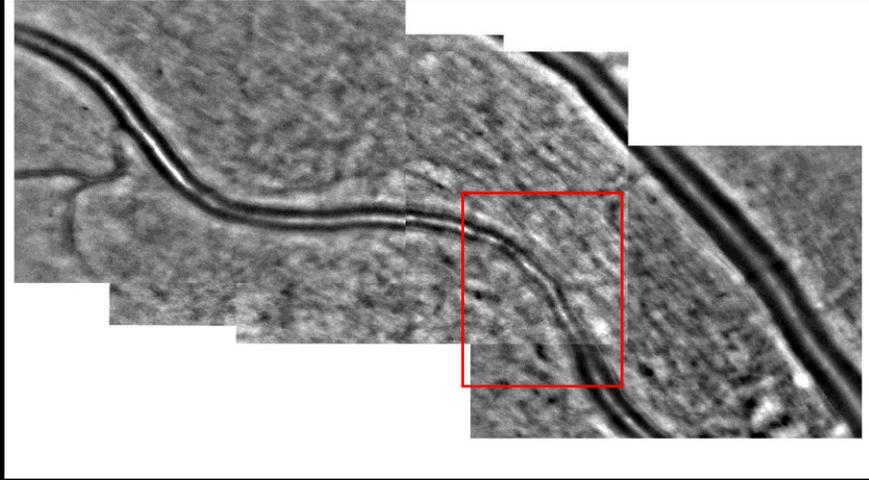


HTA chronique

Croisement artérioveineux pathologique



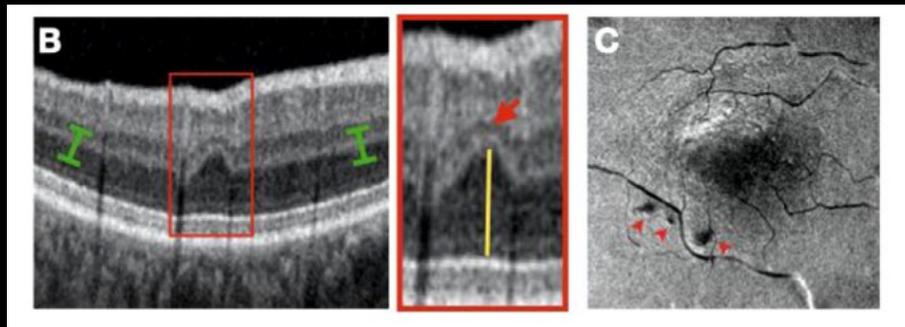
Le rétrécissement artériel focal ... est labile



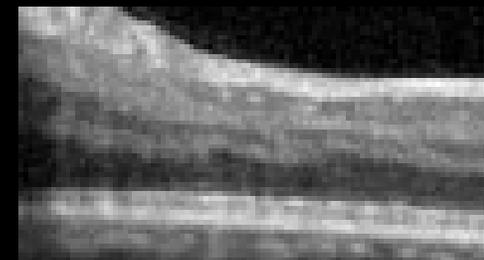
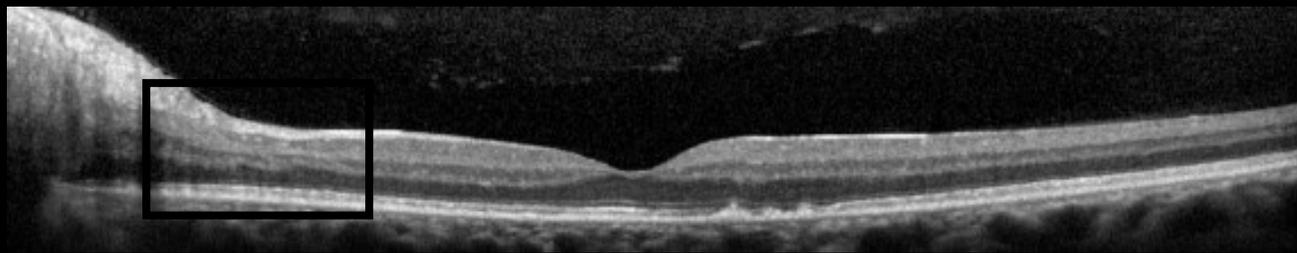
Kidney disease (IRIR study, Dr Faure, Caen)

un nouveau signe OCT des HTA chroniques:
« Retinal ischemic paravascular lesions » (RIPL)

Amincissement focal de la couche nucléaire interne + augmentation de l'épaisseur de la couche nucléaire externe sous jacente -> aspect ondulé des couches rétiniennes intermédiaires (similaire à une séquelle de PAMM)



*Infarctissements rétiniens de
petite taille*

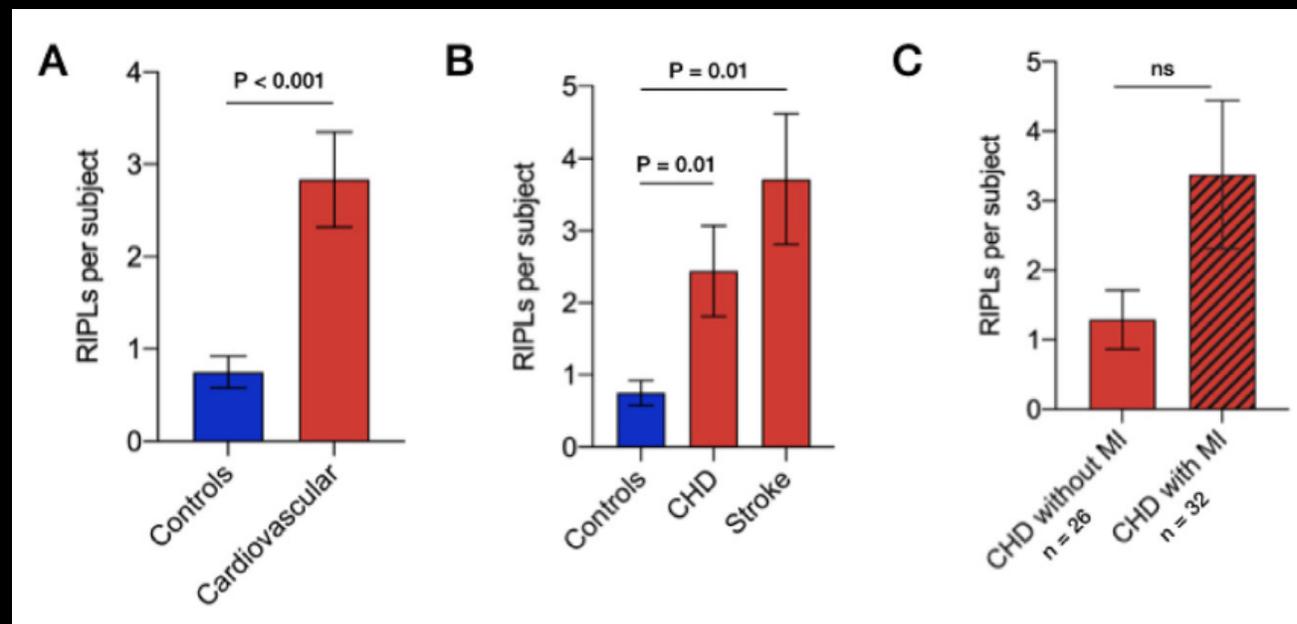


Détection des séquelles d'ischémie focale

160 individus

Cas = 26 AVC + 58 CHD

Témoins = 76 sujets sains



Statistiquement plus de RIPL dans le groupe « cardiovasculaire » que dans le groupe « sujets sains » : 2.8% vs 0.8% , p < 0.001

2,4% dans le sous-groupe CHD et 3,7% dans le sous-groupe AVC (p = 0.01 and p < 0.001, respectively)

Parmi les 58 CHD -> pas de différence significative du nombre de RIPL entre les patients avec IDM et sans IDM

Un nombre élevé de RIPL pourrait être associé à un risque cardiovasculaire plus élevé à 10 ans

RIPLs per subject	Odds ratio (95% CI)	p-value	Sensitivity	Specificity
1 or more	2.34 (1.16 – 4.74)	0.02	56.0%	67.1%
2 or more	4.17 (1.64 – 10.61)	0.003	36.9%	89.5%
3 or more	5.34 (1.71 – 16.65)	0.004	29.8%	93.4%

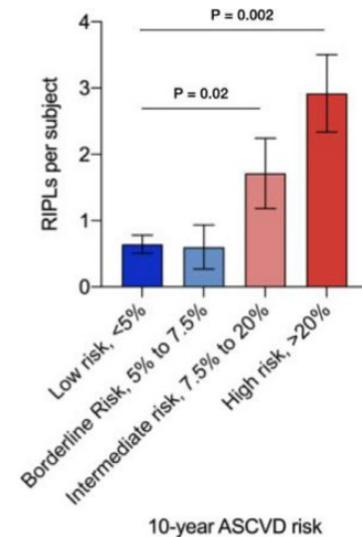
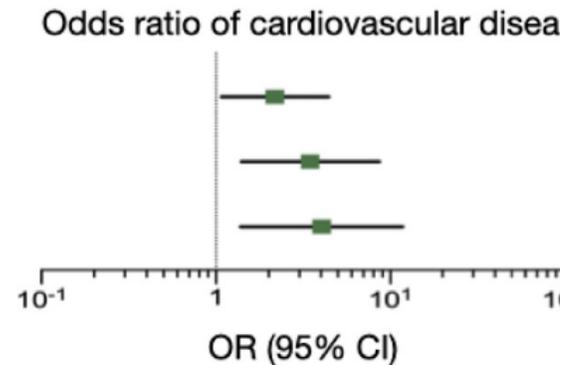
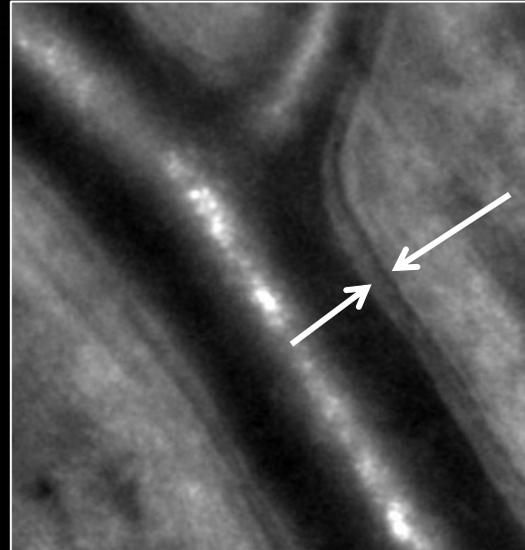
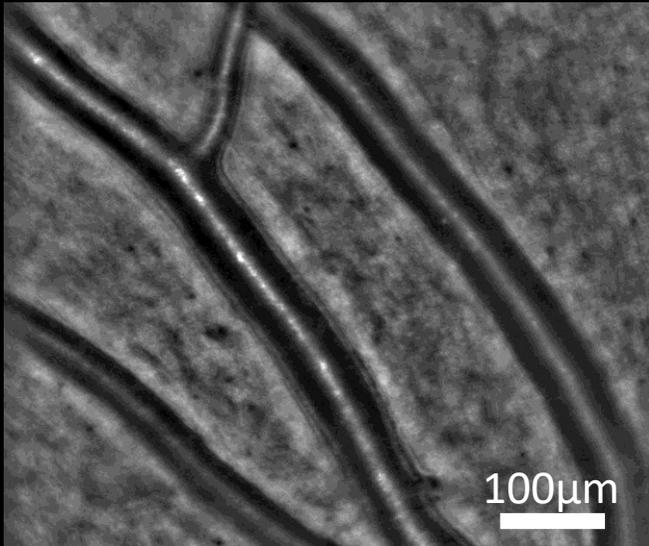
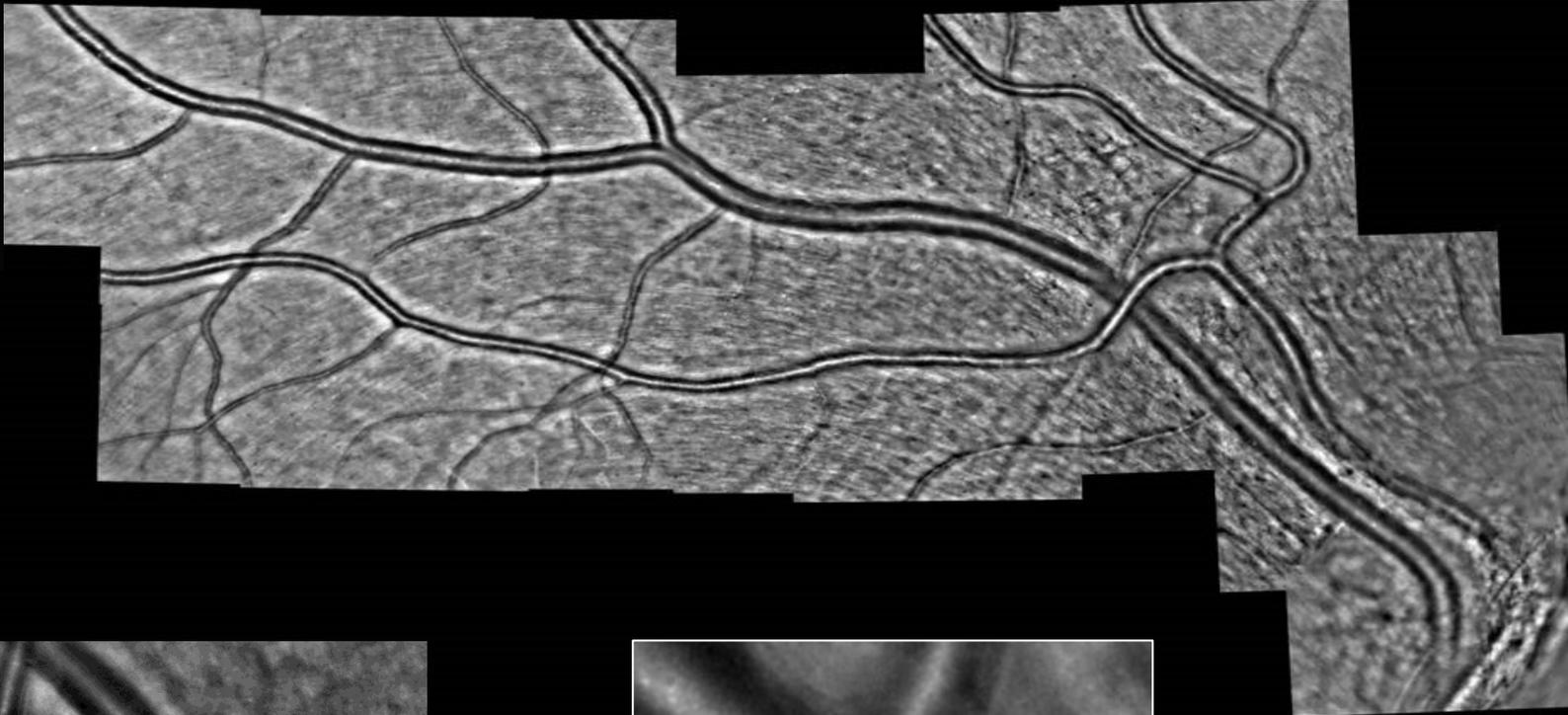
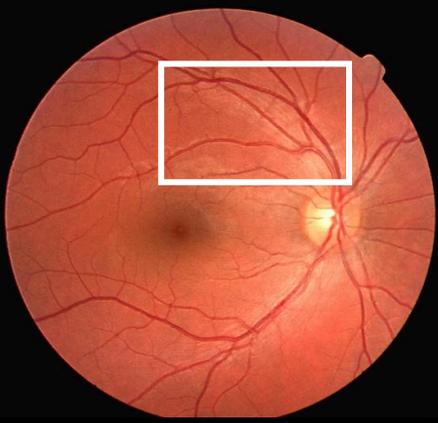
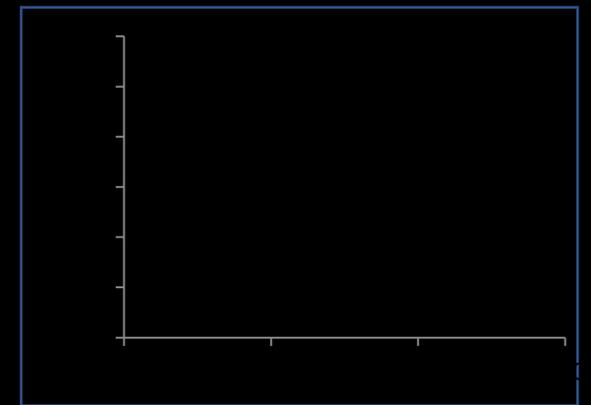
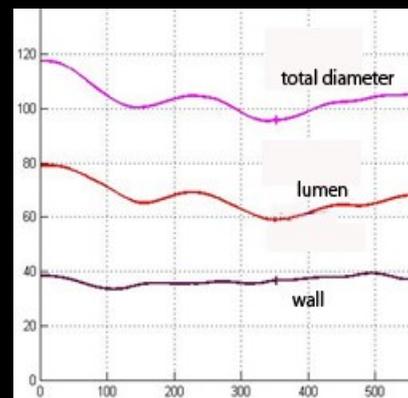
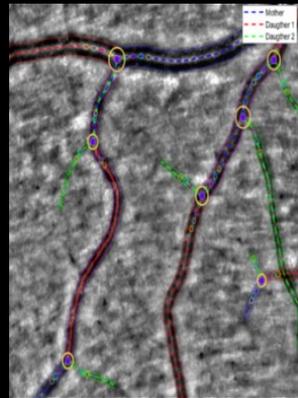
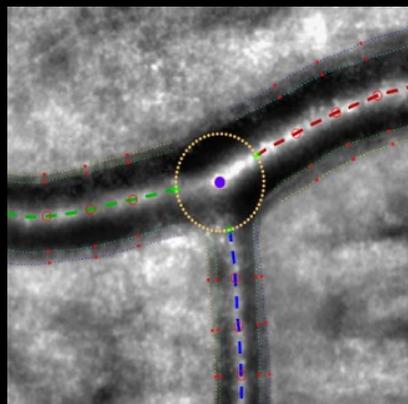
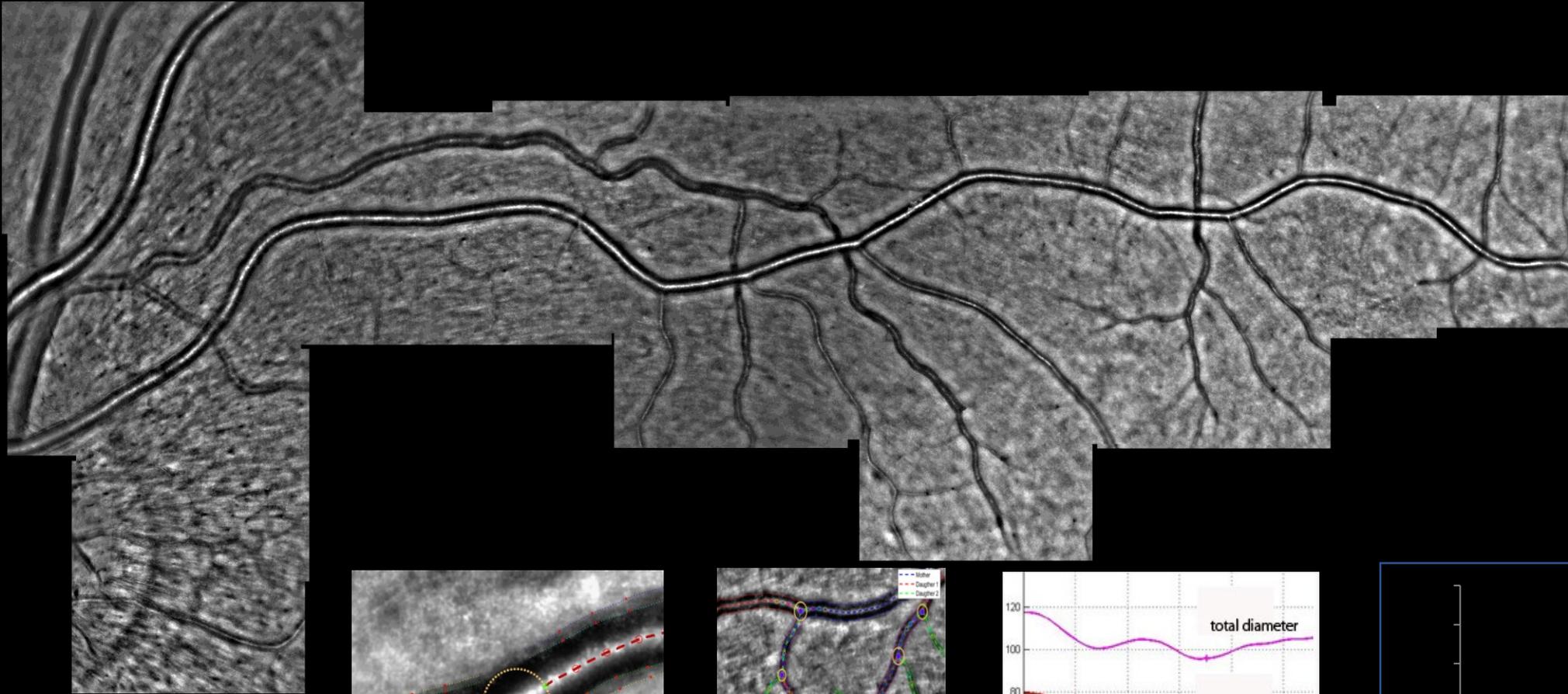
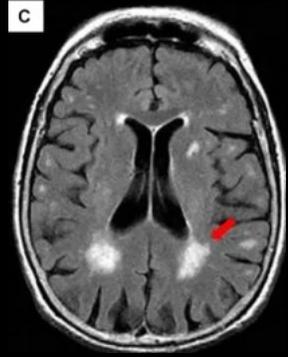


Fig. 6. Number of RIPLs per subject in individuals stratified by their 10-year ASCVD risk into 4 categories commonly used in clinical practice; low risk (<5%), borderline risk (5% to 7.5%), intermediate risk (7.5% to 20%) and high risk (>20%). Statistical significance tested using unpaired student *t*-test.

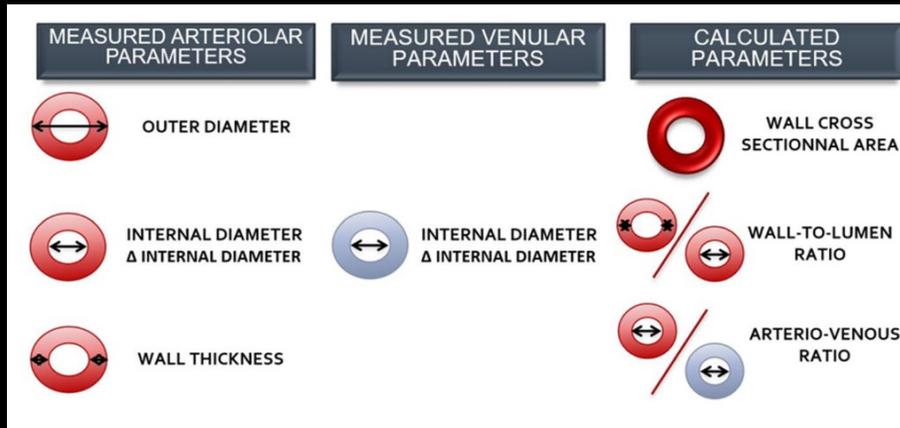
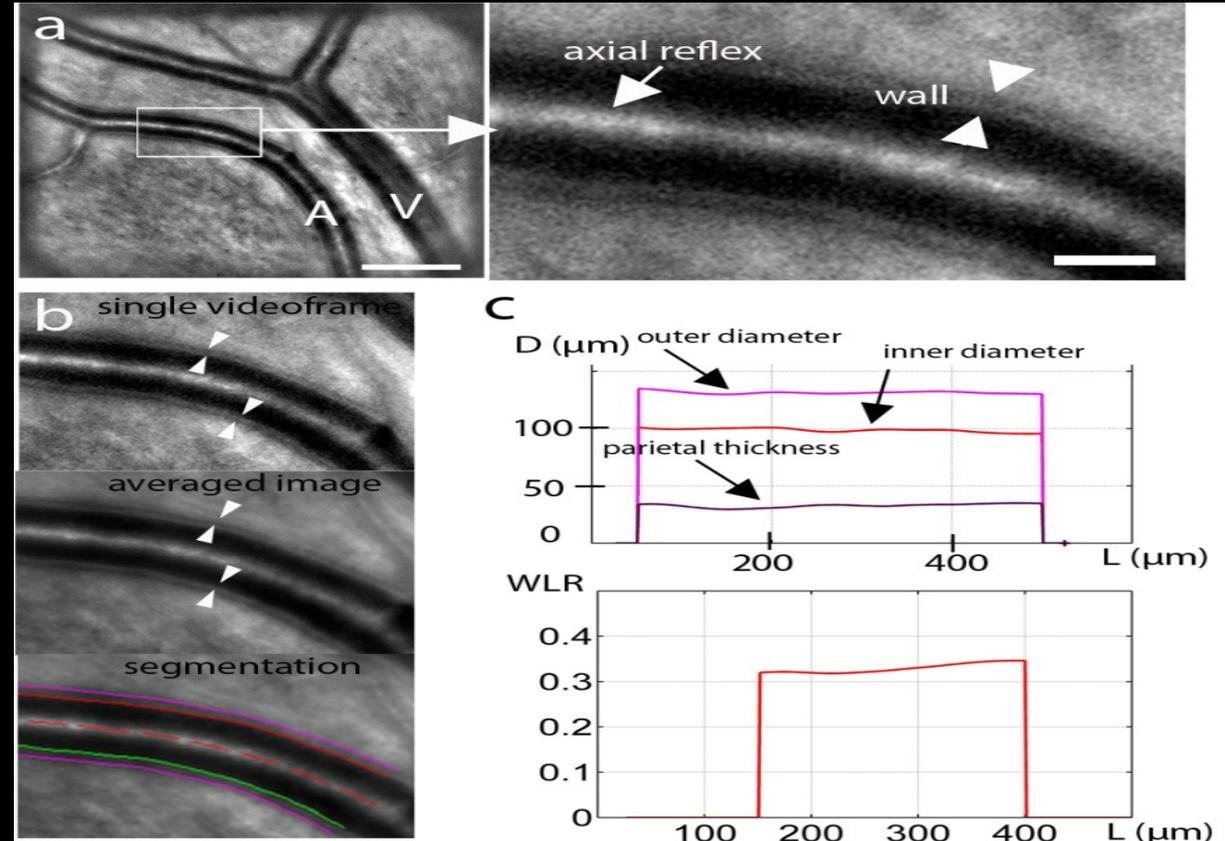
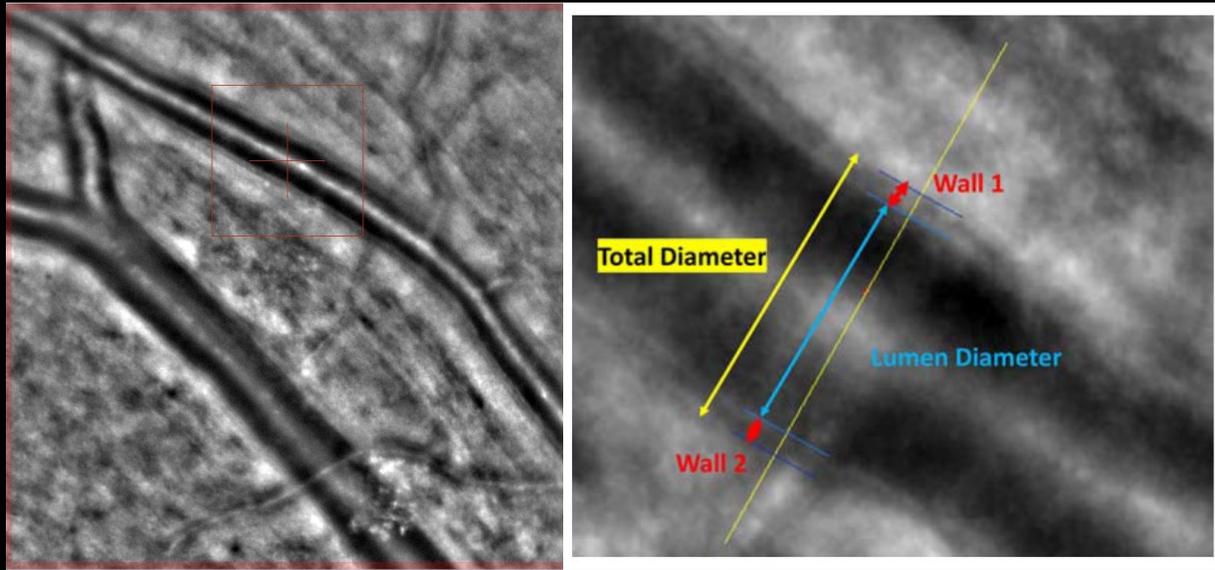
Adaptive optics ophthalmoscopy





Multiple parameters: Parietal thickness, branching coefficients, neurovascular coupling

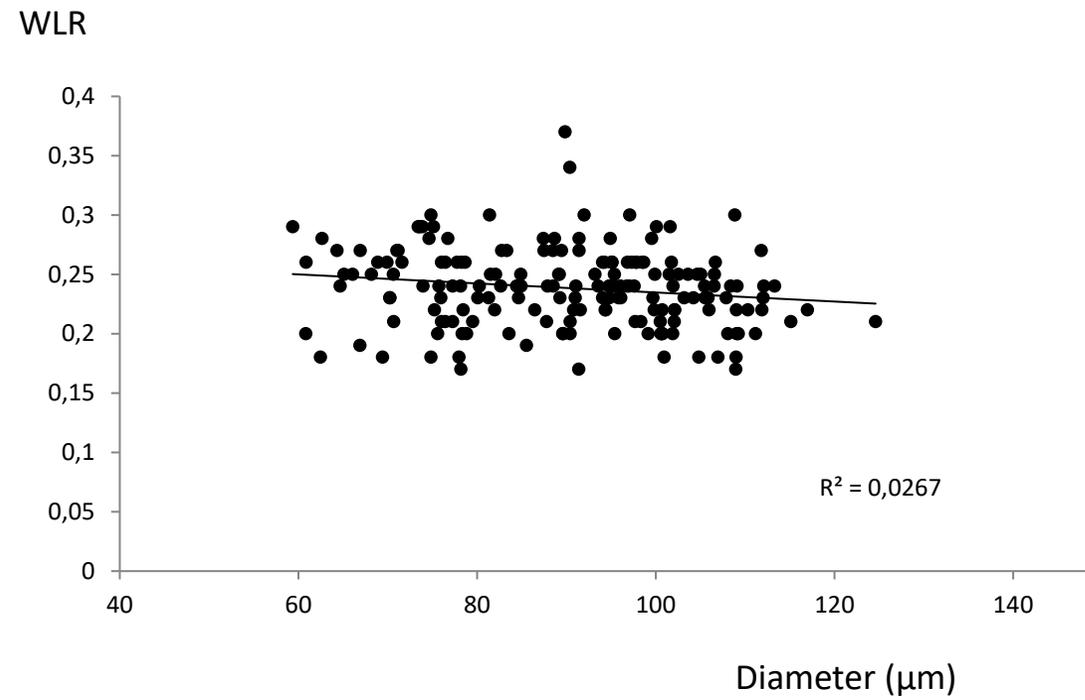
The arteriolar wall: a measurable, dimensionless biomarker



$$WLR = 1/2 (OD - ID)$$

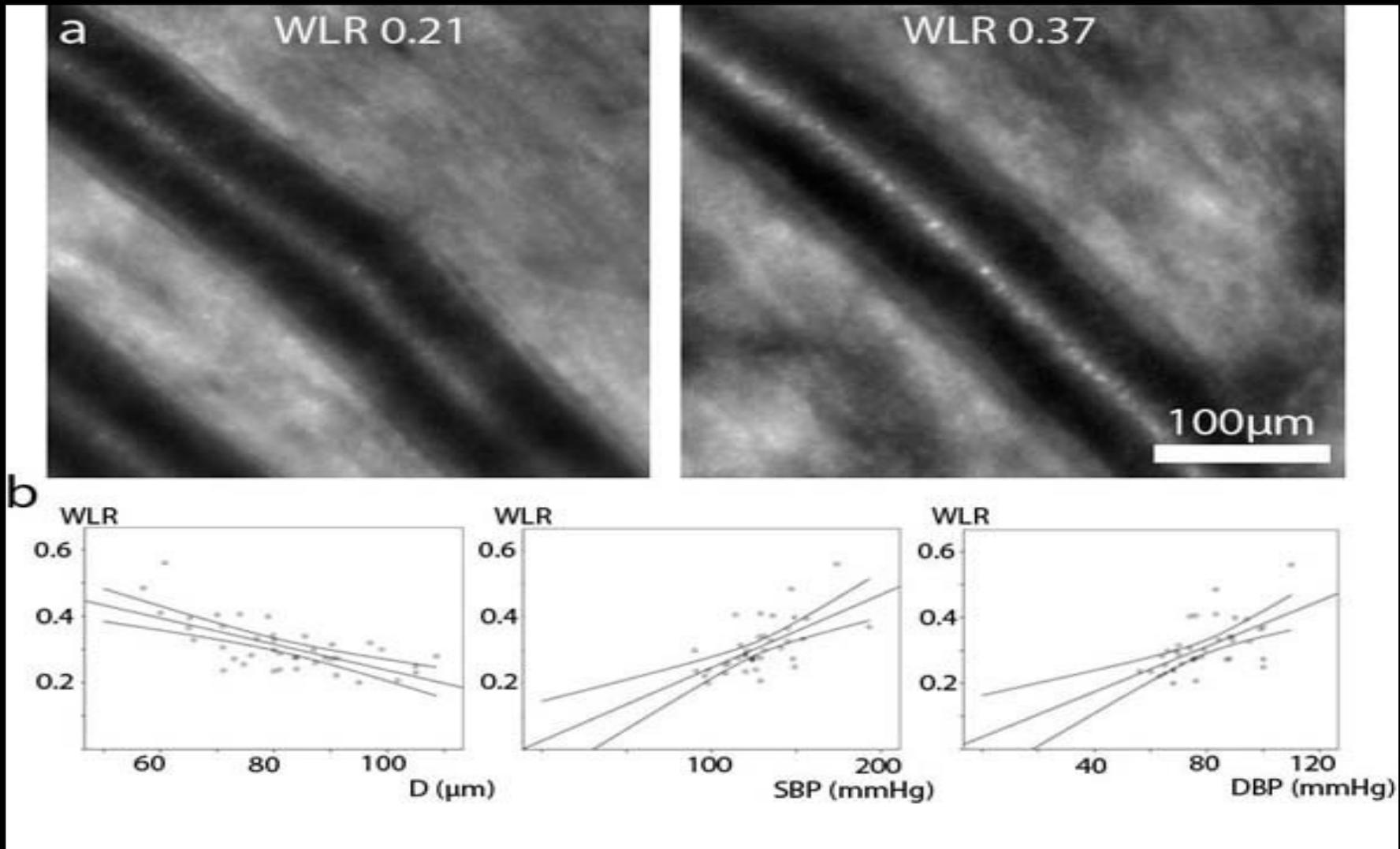
$$WCSA = \pi 4 (OD^2 - ID^2)$$

WLR chez des volontaires sains



S Debette, JF Korobelnik

La pression artérielle conditionne l'épaisseur pariétale



WLR, WCSA... Quel paramètre considérer?

- La taille d'un vaisseau est soumise à des aléas d'échantillonnage
- Le rapport paroi/lumière (« wall-to-lumen ratio », WLR) est la proportion relative de l'épaisseur pariétale sur la taille de la lumière
 - Si le vaisseau se contracte, le WLR va augmenter
 - Avantage: paramètre ne dépendant pas de la réfraction
 - Inconvénient: le WLR normal varie avec la taille du vaisseau, donc un seuil unique est difficile à établir
- Le WCSA est la surface de section en valeur réelle
 - Si le vaisseau se contracte, le WCSA ne change pas
 - Avantage: Permet théoriquement de détecter les hypertrophie pariétale
 - Inconvénient: dépend de la taille du vaisseau ET de la réfraction; de plus très sensible aux erreurs de mesures
 - D'autres paramètres sont à l'étude (asymétrie pariétale, irrégularité pariétale...)
 - Le futur: mesure à grande échelle par IA

- $WLR = 0:0051 + 0:0025 \cdot \text{mean pressure} + 0:0014 \cdot \text{age}$
which accounts for 43% of the variability of the WLR

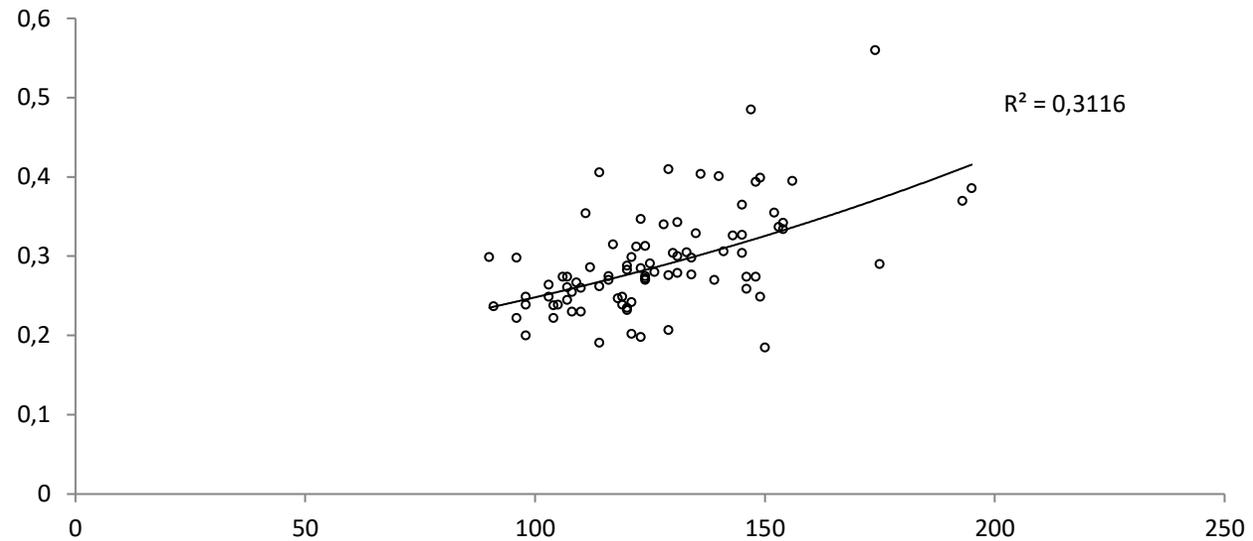
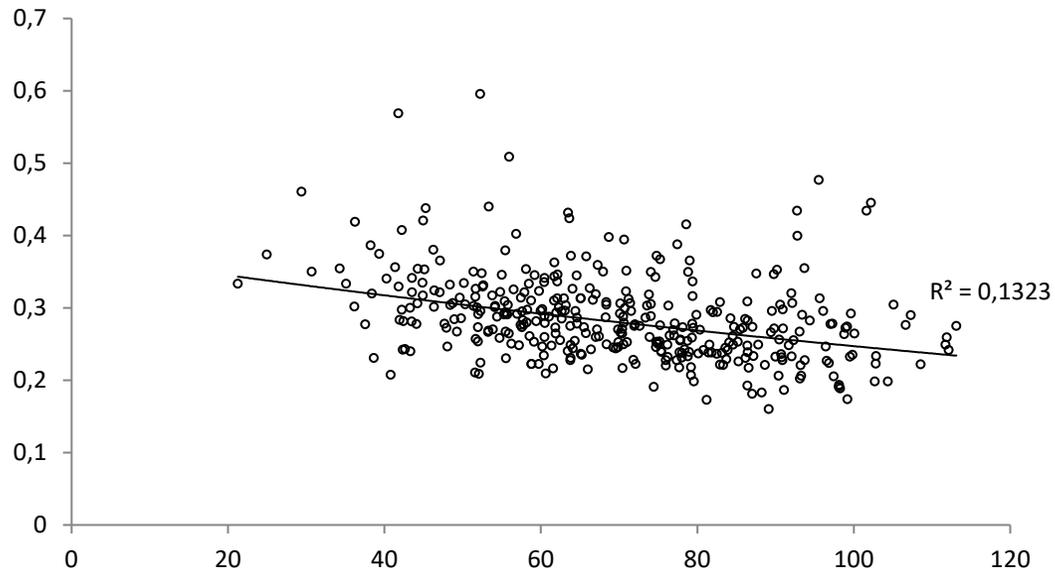
	D	P	WLR	WCSA
Age	-0.173	0.331*	0.348*	0.183
BMI	-0.254	0.241*	0.342*	0
SBP	-0.384**	0.438*	0.582**	0.13
DBP	-0.362*	0.437*	0.559**	0.06
Mean BP	-0.385**	0.453*	0.589**	0.05
Pulse pressure	-0.275	0.283	0.406**	0.01

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

paramètres quantitatifs vasculaires (1)

Table 2 AOO in the study groups (left) and age tertiles in the control group (right)

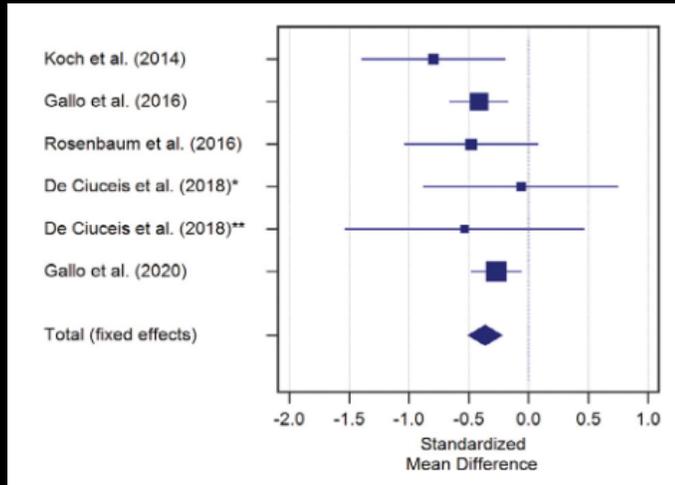
	Whole population (<i>n</i> = 429)				
	nBP/nGly (<i>n</i> = 154)	hBP/nGly (<i>n</i> = 201)	nBP/hGly (<i>n</i> = 27)	Age _{>57} /hBP/ hGly (<i>n</i> = 47)	<i>p</i>
WLR	0.253 [0.23; 0.29]	0.28 [0.25; 0.283]*	0.267 [0.23; 0.29]	0.273 [0.253; 0.297] [†]	<0.001
AVR	0.75 [0.67; 0.83]	0.71 [0.62; 0.79] [†]	0.76 [0.67; 0.88]	0.74 [0.69; 0.80]	0.012
WT, μm	23.47 [21.4;26.2]	24.87 [22.5;27.4] [†]	24.07 [23.4;26.8]	25.9 [23.8;28.8]*	<0.001
aID, μm	93.6 ± 11.6	90.2 ± 13.4 [‡]	97.7 ± 12.5	96.1 ± 12.2	0.002
CV aID, %	2.39 [1.6; 3.8]	2.69 [1.7; 4.5]	2.1 [1.3; 3.8]	2.97 [1.6; 3.7]	0.352
WCSA, μm^2	4011.6 ± 949	4105.3 ± 1053	4322.6 ± 688 [‡]	4524.7 ± 949 [†]	0.005
vID, μm	126.0 ± 17.3	127.5 ± 18.9	125.4 ± 20.5	129.9 ± 19.9	0.501
CV ID, %	2.67 [1.5; 4.1]	2.83 [1.6; 3.9]	3.23 [1.9; 4.7]	3.1 [1.9; 4.6]	0.382

(1) Non-invasive evaluation of retinal vascular remodeling and hypertrophy in humans: intricate effect of ageing, blood pressure and glycaemia Antonio Gallo^{1,2} · Thomas Dietenbeck² · Alain Giron² · Michel Paques³ · Nadjia Kachenoura² · Xavier Girerd¹, 2021

Analyse des paramètres quantitatifs vasculaires (1)

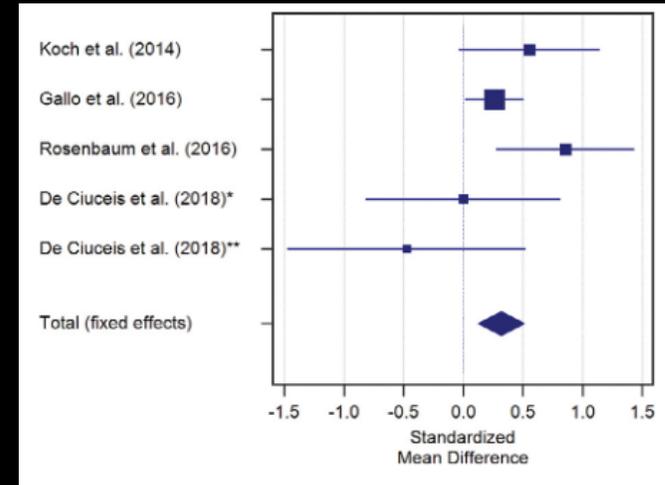
Diamètre interne

I² = 0%, P < 0.001



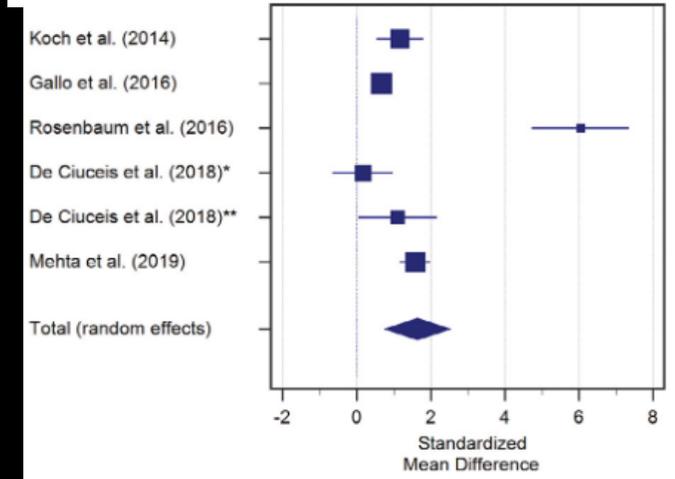
Epaisseur pariétale

I² = 49%, P = 0.002



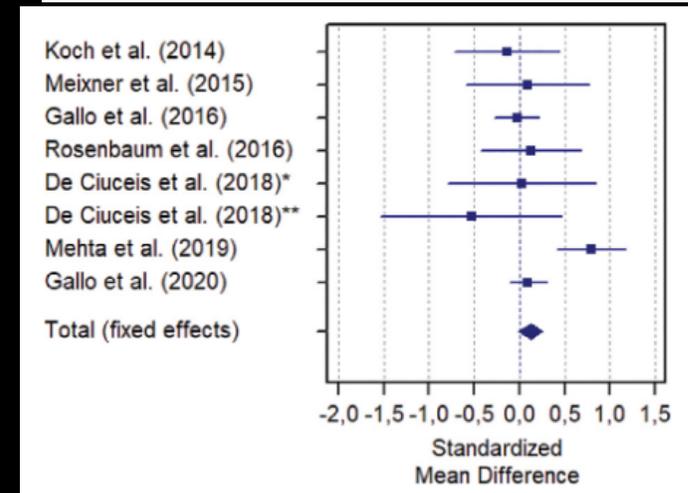
WLR

I² = 94%, P < 0.001



WCSA

I² = 58%, P = 0.07



Le WLR comme critère diagnostique de l'HTA masquée?

Table 2
Wall-to-lumen ratio and internal diameter cut-offs calculated in the 1500 subjects population.

	Cut-off	AUC	CI 95%	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
WLR	≥ 0.314	0.659	0.633–0.685	71.38	57.14	8.4	97.3
ID	< 78.251	0.624	0.597–0.651	52.47	73.21	6.6	97.7

WLR: wall-to-lumen ratio; ID: internal diameter; AUC: area under the operator receiving curve; PPV: positive predictive value; NPV: negative predictive value.

Analyse du remodelage vasculaire

- Augmentation WLR et WCSA -> remodelage hypertrophique
 - Serait plutôt associé aux élévations chronique de la TA ⁽¹⁾
- Augmentation WLR, WCSA constant -> remodelage eutrophique
 - Serait plutôt associé à des élévations rapides de la TA ⁽²⁾
- En pratique résultats discordants ⁽³⁾

(1) Wall-to-Lumen Ratio of Retinal Arterioles and Arteriole-to-Venule Ratio of Retinal Vessels in Patients with Cerebrovascular Damage Delia Baleanu,¹ Martin Ritt,² Joanna Harazny,^{1,2} Josef Heckmann,³ Roland E. Schmieder,² and Georg Michelson, 2009

(2) Measurement of retinal wall-to-lumen ratio by adaptive optics retinal camera: a clinical research Eva Meixner & Georg Michelson, 2015

(3) Morphometric analysis of retinal arterioles in control and hypertensive population using adaptive optics imaging Ruchir A Mehta, Mukund C Akkali, Chaitra Jayadev, Aishwarya Anuj, Naresh K Yadav, 2019

Paramètres vasculaires rétiniens et lésions cérébrales

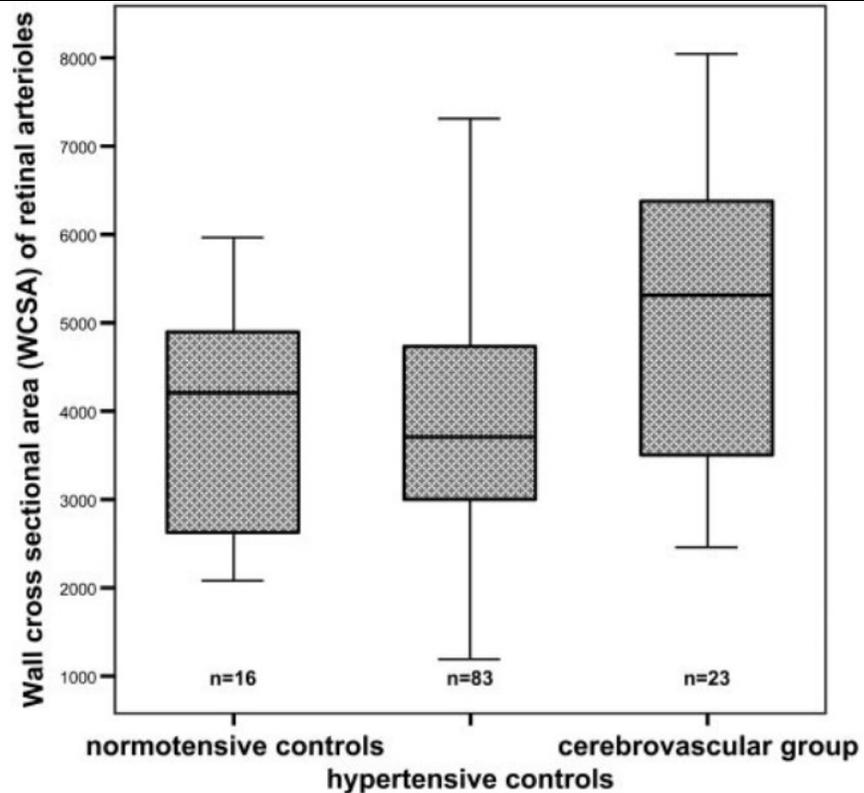
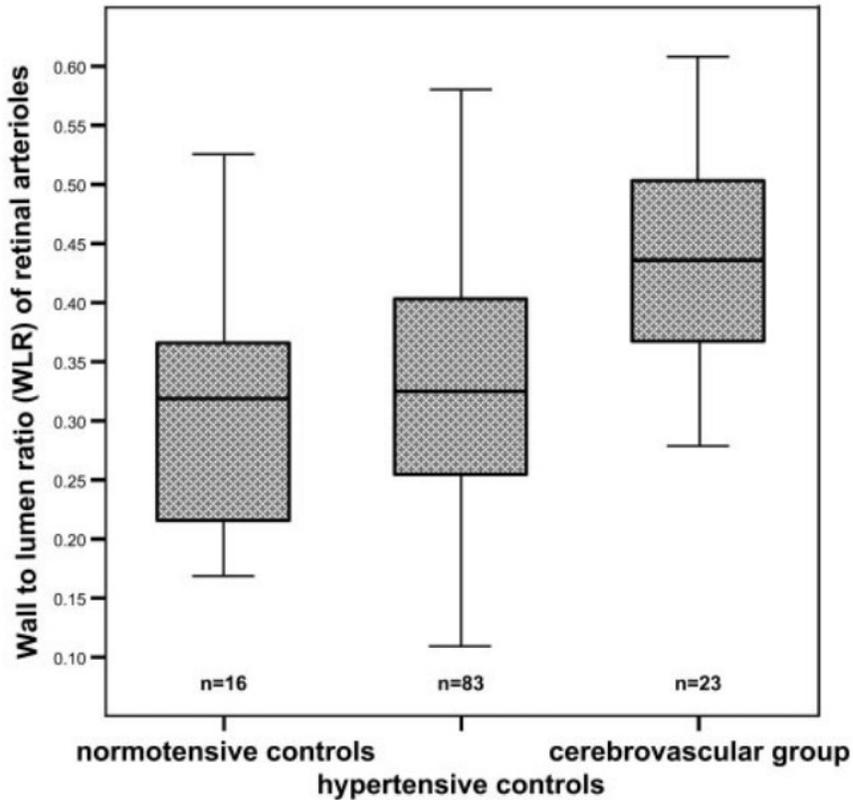
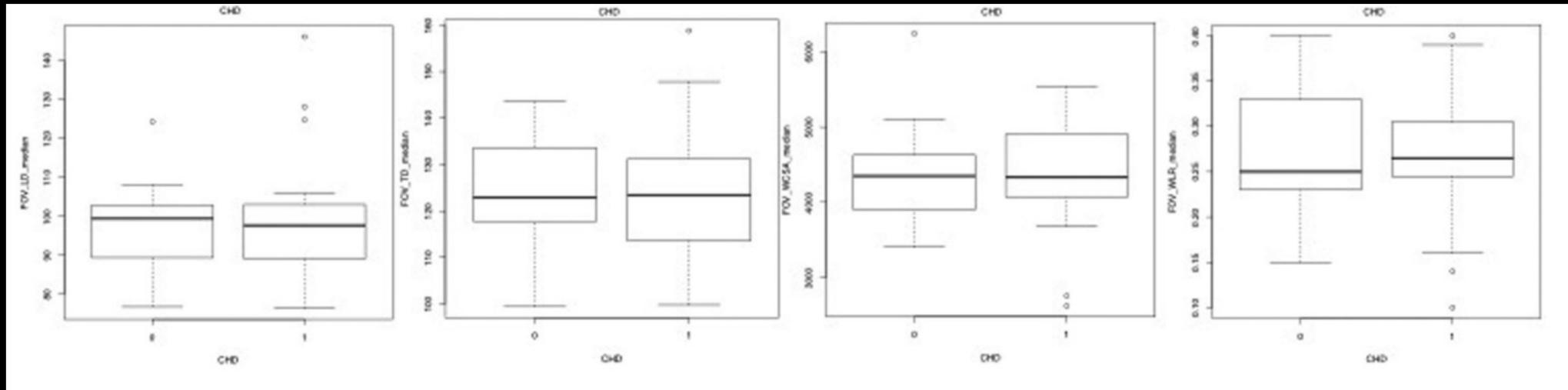


FIGURE 3. WCSA in the three study groups. WCSA was unchanged in the hypertensive control group compared with the normotensive subjects, but showed a pronounced increase in patients with cerebrovascular damage compared with both control groups, suggesting hypertrophy of retinal arteriolar wall. Data are expressed as described in Figure 1.

« This finding is in line with a previous report examining arterial structure of small arteries obtained from SC tissue that found that subjects with a growth response of vascular wall components had a higher risk of cardiovascular events than subjects without a growth response »

Paramètres vasculaires rétiniens et cardiopathie ischémique



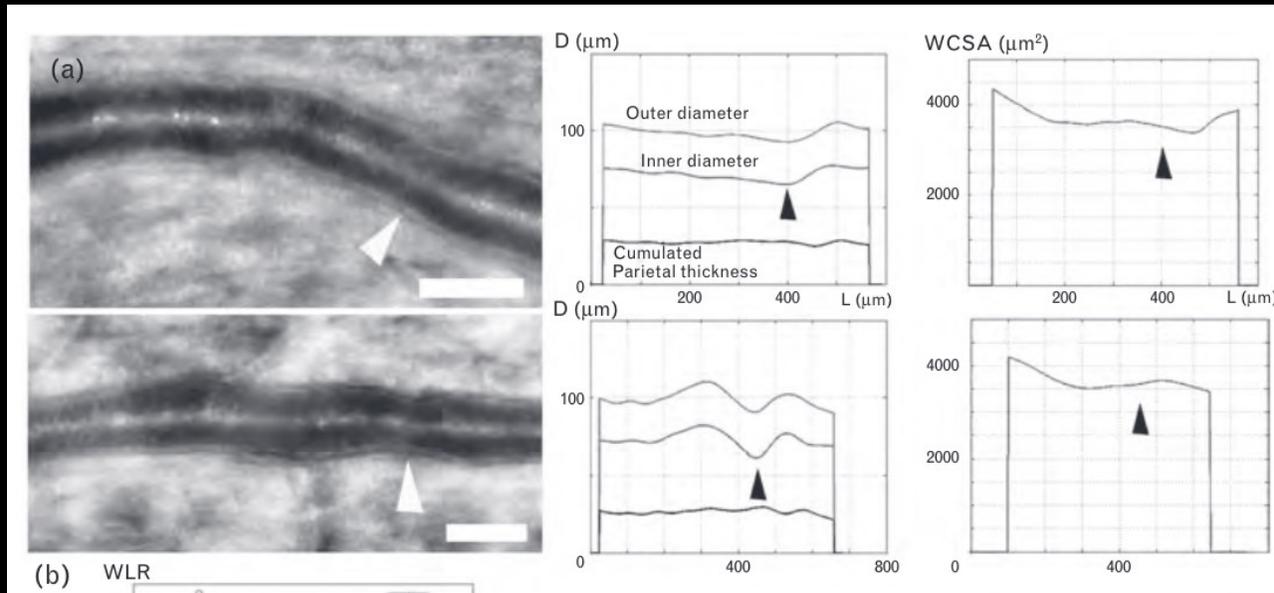
Diamètre interne

Diamètre total

WCSA

WLR

Sténoses artériolaires focales



Vasoconstriction sans augmentation de l'épaisseur pariétale

TABLE 1. Clinical and morphometric characteristics of the study population (mean \pm SD)

	Total	Normotensive	Hypertensive	P*
n	49 (23F, 26M)	30 (15F, 15M)	19 (8F, 11M)	
Age (years)	44.9 \pm 14.4	42.3 \pm 15	48 \pm 11	NS
BMI	24.9 \pm 4.7	23.8 \pm 4.5	26.4 \pm 4	NS
SBP (mmHg)	132.5 \pm 22.2	118 \pm 13	154 \pm 14	<0.01
DBP (mmHg)	82.6 \pm 14	74 \pm 9.5	95.5 \pm 10	<0.01
Mean BP (mmHg)	99 \pm 16	88.8 \pm 10	113.8 \pm 11	<0.01
Pulse BP (mmHg)	49.9 \pm 12	43.7 \pm 9	58.9 \pm 11	<0.01
D (μ m)	79.8 \pm 12	83.5 \pm 11.2	74 \pm 12.6	<0.05
P (μ m)	24.3 \pm 3.7	23.5 \pm 3.7	25.5 \pm 3.3	NS
WLR	0.31 \pm 0.07	0.285 \pm 0.05	0.36 \pm 0.08	<0.01
WCSA (μ m ²)	3411 \pm 874	3459 \pm 915	3338 \pm 826	NS

BP, blood pressure; D, diameter; NS, not statistically significant; P, parietal thickness; WCSA, wall cross-sectional surface; WLR, wall-to-lumen ratio.

*Between normo and hypertensive.

(1) Morphometric analysis of small arteries in the human retina using adaptive optics imaging: relationship with blood pressure and focal vascular changes

Classifications

Grade	Stage	Description	Ocular symptoms	Systemic involvement
1	Mild hypertension	Mild generalised arteriolar narrowing or sclerosis	No symptoms	None
2	More marked hypertension	Definite focal narrowing and arteriovenous crossings. Moderate to marked sclerosis of the retinal arterioles. Exaggerated arterial light reflex	No symptoms	None or minimal
3	Mild angiospatic retinopathy	Retinal haemorrhages, exudates and cotton wool spots. Sclerosis and spastic lesions of retinal arterioles	May be symptomatic	Cardiac, cerebral or renal dysfunction are frequently identifiable
4	Severe hypertensive retinopathy	Severe Grade III signs and papilledema. Elschnig's spots are present in some	Symptomatic	Cardiac, cerebral and renal dysfunction are more severe

The first classification of hypertensive retinopathy, proposed in 1939 by Keith, Wagener and Barker, based on the progressive severity of ophthalmoscopic signs.

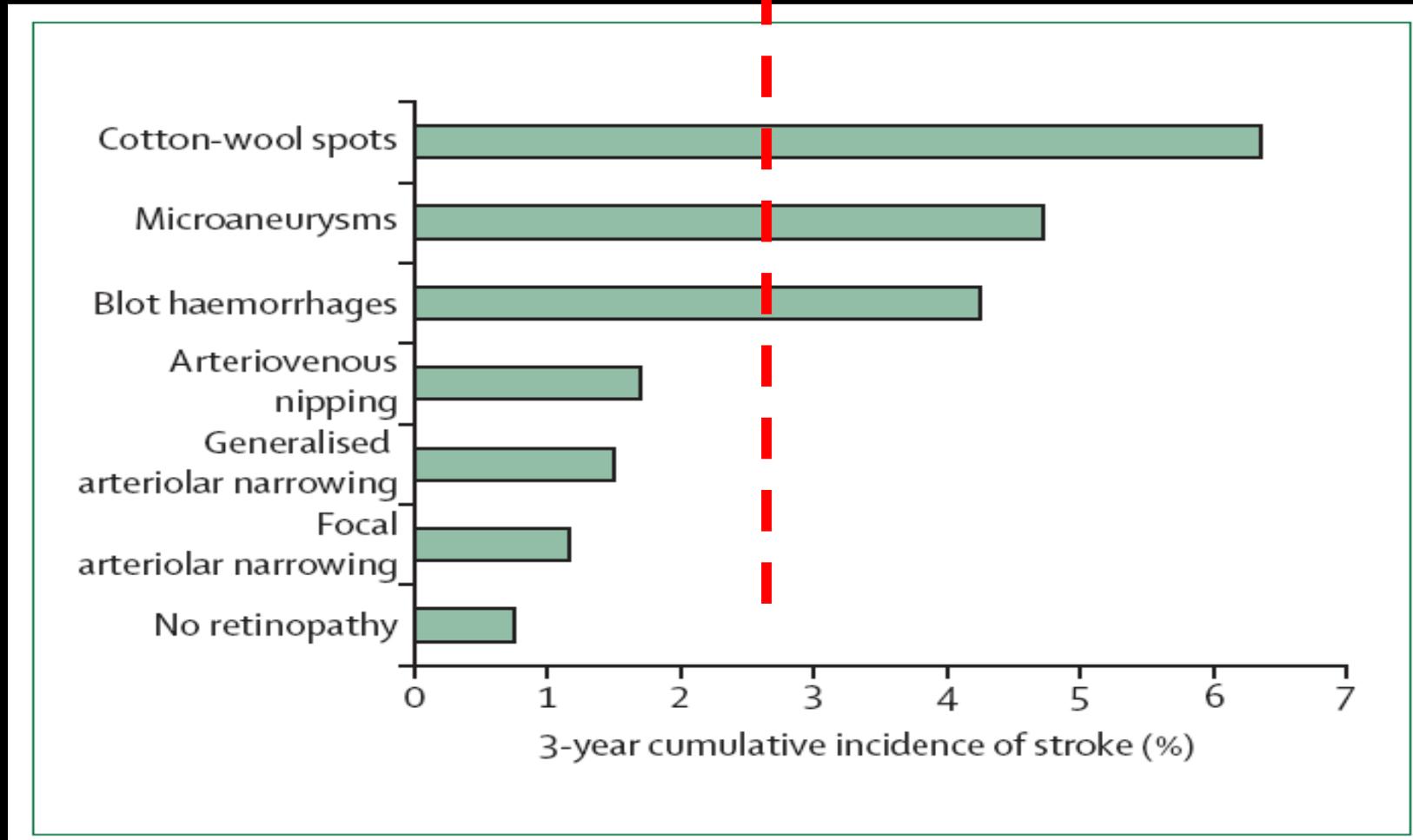
First Bibliographic Reference: Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and their prognosis. Am J Med Sci 1939;197:332-43.

Grade	Stage	Ophthalmoscopic signs	Systemic associations
1	Mild retinopathy	One or more of the following arteriolar signs: - Generalised arteriolar narrowing - Focal arteriolar narrowing - Arteriovenous nicking - Arteriolar wall opacity (silver wiring)	Modest association (risk and odd ratios of >1 but <2) with risk of clinical stroke, subclinical stroke, coronary heart disease and mortality
2	Moderate retinopathy	One or more of the following arteriolar signs: - Haemorrhage (blot, dot or flame shaped) - Microaneurysm - Cottonwool spot - Hard exudates	Strong association (risk and odds ratios of >2) with risk of clinical stroke, subclinical stroke, cognitive decline and cardiovascular mortality
3	Malignant retinopathy	Moderate retinopathy plus optic disc swelling	Strong association with mortality

A Keith-Wagener-Barret simplified three-grade classification scheme, proposed by Wong and Mitchell (2004), based on the strength of the reported associations between hypertensive retinopathy and cardiovascular risk.

R. minime

R. modérée



Synthèse des résultats

- L'OOA permet une analyse morphométrique fine des phénomènes vasomoteurs affectant la microcirculation au cours de l'HTA
- Dans les suites d'une HTA maligne, la plupart des patients n'améliorent pas leur WLR (voire l'aggravent) malgré la normalisation tensionnelle
 - des sténoses focales peuvent apparaître
 - Les deux yeux évoluent de façon parallèle, suggérant l'interventions de médiateurs humoraux (absence d'innervation vasculaire)
- Ceci suggère un découplage temporel entre pression artérielle et WLR
- Futures travaux
 - Exploration des relations entre les phénomènes post-critiques et la survenue de complications tardive (p.ex cérébrales)
 - améliorations technologiques de l'imagerie (WCSA enfin fiable?)
 - Identification de biomarqueurs pertinents pour le suivi thérapeutique

In vivo morphometry of retinal microvessels



Sophie Bonnin, MD

Capillary perfusion plays a crucial role in retinal diseases such as diabetic retinopathy; however, capillary hemodynamics remains poorly known.

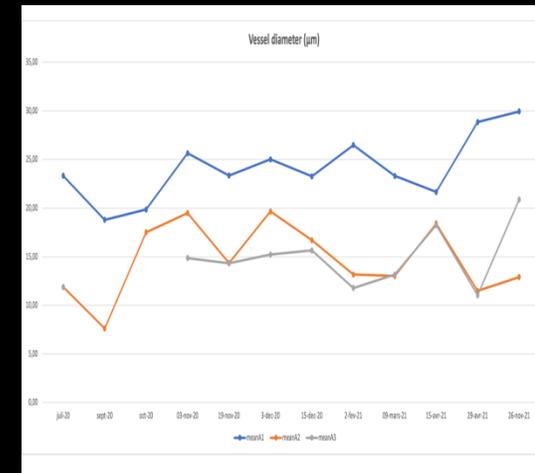
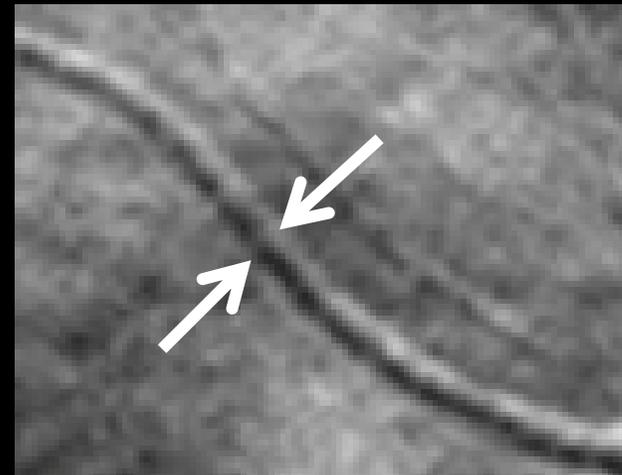
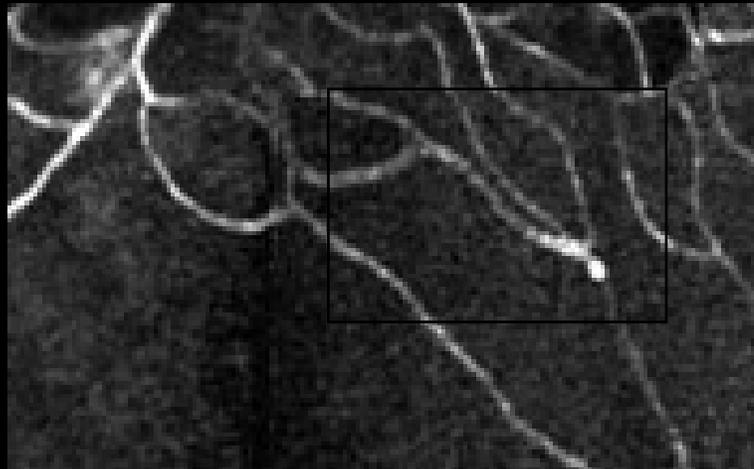
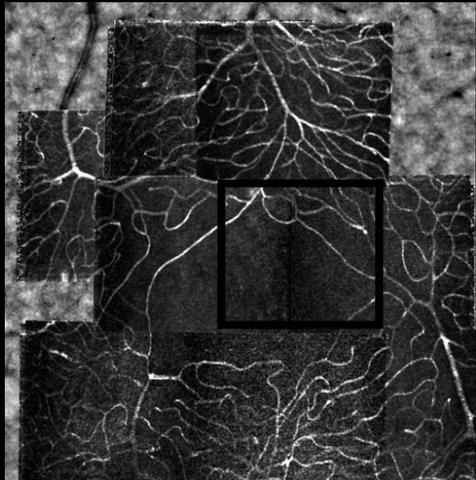
My goal: to analyze the evolution of capillary perfusion and its possible implication in microvascular diseases

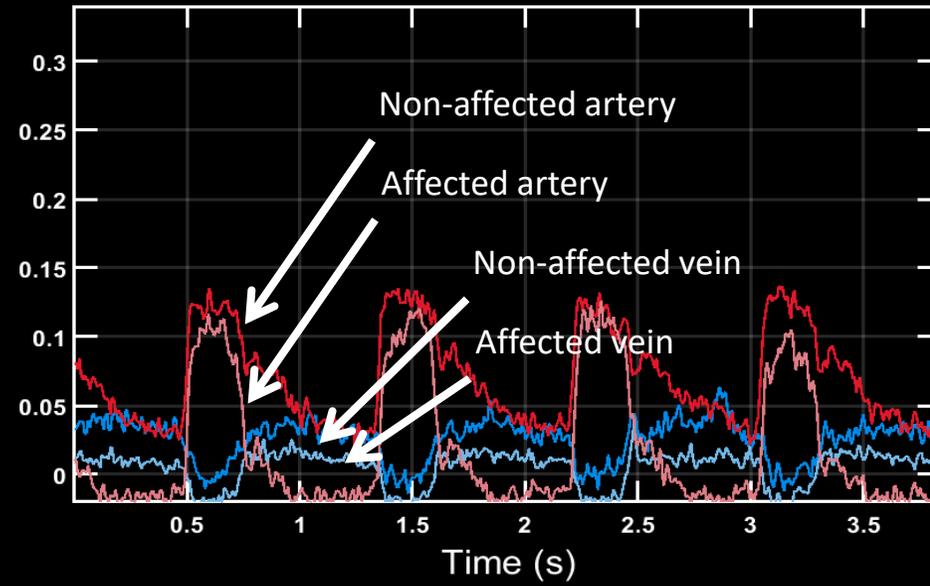
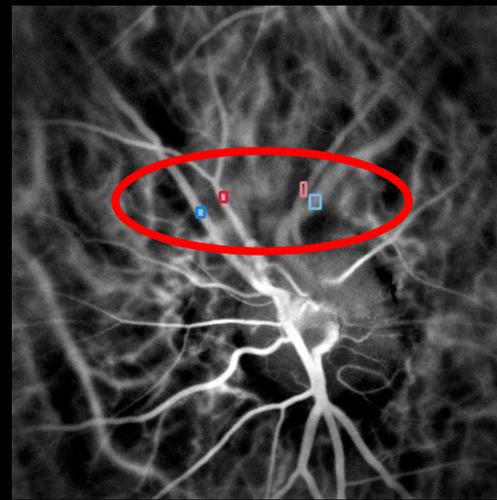
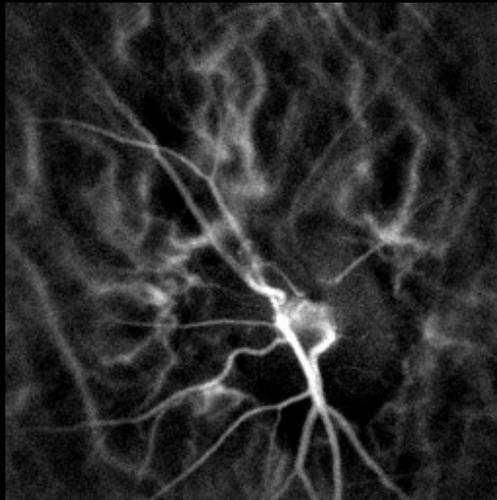
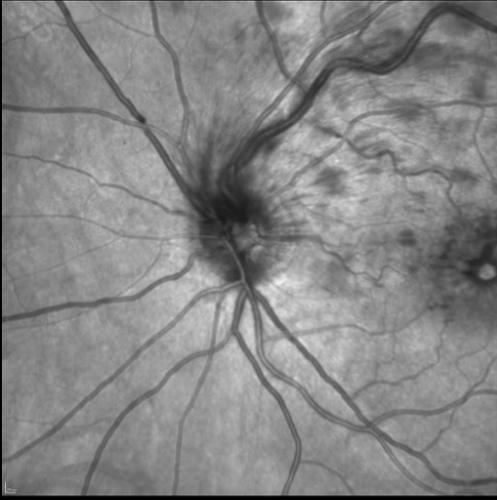
My approach: longitudinal multimodal AOSLO imaging for morphometry of microvessels

Mentors:

Aude COUTURIER

Michel PAQUES

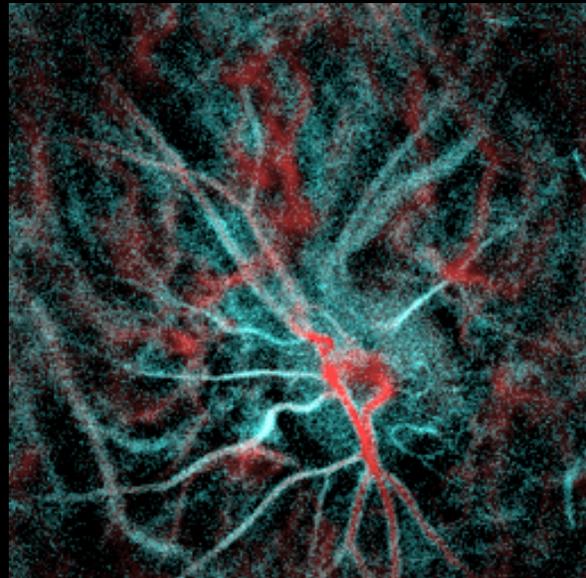
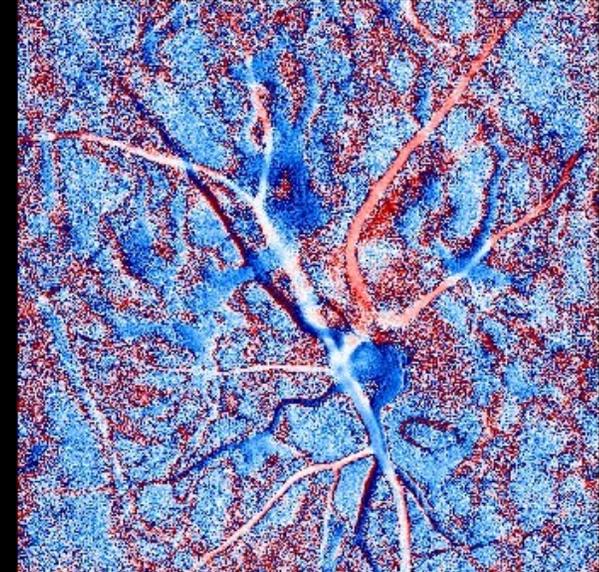




Systole / Diastole

Low flow / high flow

• Composite movie



Conclusion

- La sémiologie rétinienne de l'HTA maligne s'est enrichie de l'apport de l'OCT et de l'OOA; de nouvelles imageries sont en développement
- WLR = premier biomarqueur quantitatif et évolutif du retentissement microvasculaire de l'HTA
- L'HTA est responsable de ***phénomènes vasomoteurs*** observables au niveau rétinien
- Les nouvelles imageries ont révélé la fréquence des ***occlusions artériolaires per et post-HTA maligne***
 - Ces phénomènes sont évolutifs pendant plusieurs mois malgré la rééquilibration tensionnelle

Détection des séquelles d'ischémie focale

Après analyse multivariée, la présence de RIPL à l'OCT est associée à un risque cardiovasculaire accru

