Morphometric examination of retinal microcirculation using high resolution imaging in patients with multiple sclerosis

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Multiple sclerosis (MS) shows a hypoxic-like pattern (III), accumulate lesions in watershed areas and areas of high vessels density, and have a more aggressive progression when associated with cardio-vascular risk factors (Haider et al., 2016, Brain). Furthermore, MS patients' brain and retina have a decreased blood flow (Jiang et al., 2016, Multiple Sclerosis Journal). Whether it truly represents a pathological phenomenon remains debated. Blood flow depends strongly on the resistance of the microcirculation and hence, plausibly, on venules and arterioles remodeling. Then, a precise examination for microvascular systemic contribution is necessary.

The aim of the present study is to compare morphometric remodeling of retinal small vessels in MS patients and controls

Method

- 20 patients (40.2 mean age ± 11.5 sd; 15 female) and 20 paired matched control subjects (37.4 mean age ± 10.3 sd; 11 female), aged 18 to 62 years, without cardiovascular risk factors or previous history of optic neuritis, were included for prospective analysis (clinical trial: NCT03508089). Fifteen patients had RRMS, for had SPMS and one PPMS (Tab 1).
- Blind semi-automated analysis of retinal vessels morphometric measures was realized independently on both eyes, using adaptive optics (A.O.) imaging (Rtx1®, Orsay, France) **Fig1.** Wall-to-lumen ratio was also analyzed, it is a highly sensitive marker classically used in small vessels disease analysis and only depictable with device harboring micrometric resolution or by pathology examination. It has the advantage to be independent from refractory aberrations (Koch et al., 2014, Journal of Hypertension).
- Linear mixed models were used to compare measurements of retinal arteries and venules between groups. These models allowed to take into account the correlations between eyes within the same subject.

Tab 1. *Baseline demographics for controls and patients included in the analyses.*

	Controls (mean ± sd)	Patients (mean ± sd)
Tabaco smoking	7	5
Weight	74.7 ± 25.6	67.8 ± 11
Height	170.9 ± 7.3	169.6 ± 6.3
BMI	25.3 ± 6.4	23.3 ± 3.9
SBP	119.7 ± 14	118.1 ± 13.1
DBP	68.1 ± 11.7	66.8 ± 8.3
HR	78.8 ± 8.9	69.9 ± 12.6
Disease duration	NA	13 ± 10
EDSS	NA	2.5 ± 2

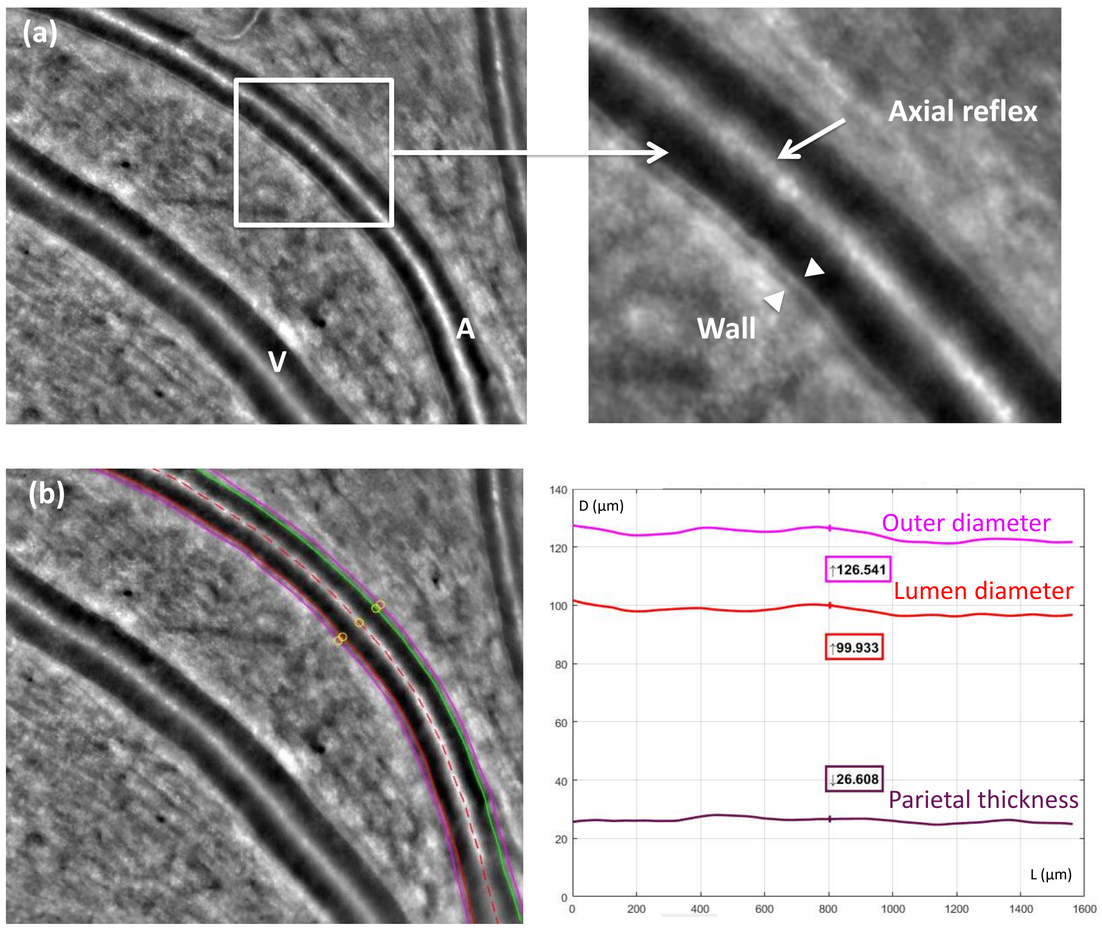

Fig 1. *Adaptive optics image and segmentation of a retinal arteriole. (a) Video acquired image (enlargement on right). Note that wall structures are visible (between the arrow) (A: arteriole, V : venule). (b) Segmentation with morphogram of the segmented arteriole (D : diameter, L : length).*

Results

No statistical difference was found between controls and MS patients for all the morphometrics parameters evaluated **Tab2**.

Tab 2. *Quantification of retinal arterio-venous microcirculation characteristics*

	Controls (n=20)	Patients (n=20)	Pr > |t|
Arteriole inner diameter	98.3 ± 3.5	100.4 ± 3.6	**0.68**
Arteriolar wall thickness	26.3 ± 0.9	28.1 ± 1	**0.19**
Wall / Lumen ratio	0.28 ± 0.01	0.29 ± 0.01	**0.39**
Venule inner diameter	138.6 ± 6.7	136.4 ± 7.2	**0.75**
Artery / Vein lumen ratio	0.72 ± 0.04	0.75 ± 0.04	**0.58**

Discussion

A.O. has a spatial resolution comparable with microscopy (*i.e.* 2 microns). It is then extremely sensitive to early signs of arteriolar remodeling and is therefore increasingly used to study small vessels disease (Rosenbaum et al., 2016, Journal of Hypertension). Albeit, we did not find any subtle signs of arteriolar remodeling. Arteriolar remodeling might for example be expected in reaction to a downstream resistance alteration or to an excess of vasoconstrictive hormones. We neither found any signs of retinal venous congestion, as expected (Comi et al., 2013, Multiple Sclerosis Journal). Two main hypotheses can explain our results: this pilot study was underpowered to detect small differences ; there is no modification of the retinal microcirculation in MS patients and complementary hypothesis should be proposed to explain hemodynamics alteration in MS, at least in the retina.

Conclusion

The present study does not support a remodeling of retinal arterio-venous microcirculation in patients with MS. However, further studies are needed.

Conflicts of interest: none

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