Ultra high resolution 3D microangiography of the rat ocular circulation at 11.7 T

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INTRODUCTION Ocular circulation plays a crucial role in maintaining the function of the eye and the retina. The retina is supplied by two distinct vasculatures, the retinal and choroidal circulations. The retinal vessels are located on the retinal surface, embedded within the ganglion cell and inner nuclear cell layers. The choroidal vessels are located behind the retinal pigment epithelium. In between where the photoreceptor layer (~100 micron thick) reside, there are no blood vessels. The total thickness of the retina, including the choroid, is about 270 μm [1]. 2D fluorescein angiography [2] enhanced by optical fluorescein dye has been used to visualize vessels of the retina but is depth ambiguous. Here, we developed and applied a novel 3D MR microangiography (μMRA) with a nominal 35 μm isotropic resolution to image the vasculature of the rat eye at 11.7 T. An in-house 3D flatterening algorithm was developed to visualize vasculature of the retina in any orientation. Pre-MION (monocrystalline iron oxide nanoparticle) provided contrast of the arterial trees and post-MION provide arterial and venous vessels. Moreover, functional μMRA was investigated during oxygen and carbogen challenges relative to air.

METHODS Four rats were anesthetized with 1.1% isoflurane, mechanically ventilated, paralyzed with pancuronium bromide (4 mg/kg first dose, 4 mg/kg/hr, i.v.). Atropine eye drop was applied topically to dilate the pupil and reduce the motion artifact at the anterior part of the eye. μMRA was performed before and after MION (30 mg Fe/kg, i.v.) injection. μMRA was also performed during oxygen and carbogen (95%O_2+5%CO_2) breathing relative to air. A small surface coil (ID~7 mm) was placed on the left eye. Shimming used FASTMAP on an isotropic voxel of 7x7x7 mm, encompassing the entire eye. High resolution 3D gradient-echo with flow compensation (GEFC) MRI was measured using spectral width = 60 kHz, TR = 26 ms, TE = 4.3 ms, FOV = 9x9x9 mm, acquisition matrix = 256x256x256 (with half fourier, zero-filling acceleration of 2 and 4 in X and Z direction, respectively), yielding a nominal isotropic resolution = 35×35×35 μm. The retina was flattened using codes written in Matlab into 2D for different layers to present in an en face view.

RESULT & DISCUSSION We developed an ultra high resolution 3D microangiographic technique to depict microvascular structures of the rat eye. The major findings are: (i) Central retinal artery and long posterior ciliary arteries can be seen on 3D GEFC MRI (pre-MION contrast). (ii) MION improved the vascular contrast of the entire ocular circulation, making the retinal vessels and choroid more readily identifiable. (iii) The 3D eyeball flattening technique enabled isolation of the vascular pattern at different depth of the retinal thickness. (iv) Functional μMRA showed ocular vessel signal enhancement during oxygen or carbogen inhalation. Oxygen inhalation enhanced retinal, choroidal, and outside retinal circulation by 11.75, 10.44, and 8.39%, respectively, while carbogen enhanced 15.43, 11.97, and 8.27%, respectively (n = 2). Retinal arteries and veins can also be distinguished by oxygen or carbogen challenges. In contrast to the radially projecting retinal vessels, the choroid layer showed no apparent vascular structure on the flattened map although μMRA signals were elevated relative to background. This is because of the dense and randomly oriented vascular network composed of choriocapillaris behind the retinal pigment epithelium and the large choroid vessels behind the choroiocapillaris. Only the long posterior ciliary arteries at the posterior retina that support the choroidal arterioles and choriocapillaris [3] can be reliably detected. Gas challenge data demonstrated the retinal vascular layer was more responsive to hypercapnia compared with choroid, consistent to those reported previously [4,5].

CONCLUSION The present study is the first report of in vivo μMRA of the eye at high spatial resolution with layer specificity. Oxygen and carbogen breathing enhance μMRA signals. Future studies will focus on (1) pushing spatiotemporal resolution of the ocular μMRA, (2) combining functional MRI to investigate ocular vascular functions, (3) applying to animal models with ocular vascular disorders, and (4) translating these approaches to humans.

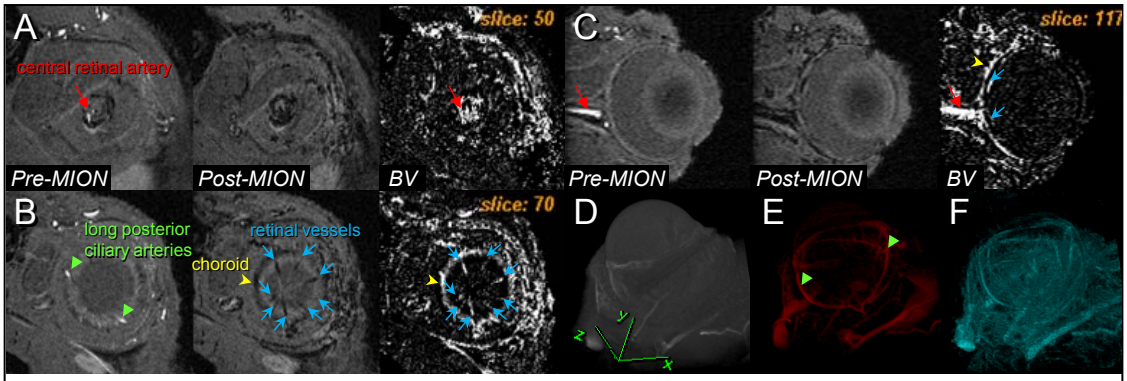

Fig 1. 3D μMRA reveals vascular morphology of a rat eye. **(A)** Images in axial view cutting through the optic nerve head. High-resolution blood volume (BV) contrast was derived from pre- and post-MION images. **(B)** Images slightly more anterior to (A), showing the retinal vessels branching from the central retinal artery. **(C)** Sagittal views of the eye depict the central retinal artery, choroid, and the retinal vessels. **(D)** Volume rendering of a 3D eyeball embedded in surrounding tissue. 3D surface rendering of the vascular structure **(E)** before and **(F)** MION injection. *Red arrows: central retinal artery; blue arrows: retinal vessels; green arrowheads: long posterior ciliary arteries; yellow arrowheads: choroid.*

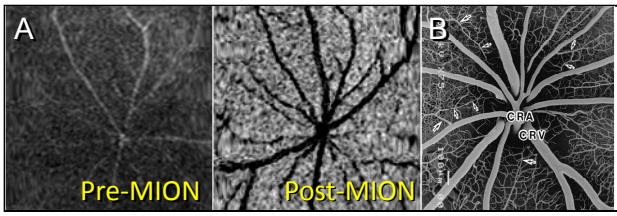

Fig 2. Flattened retinal vascular layer. **(A)** Contrast before and after MION injection. **(B)** Electron micrograph of a rat eye using postmortem corrosion casts from [3]. MRI reveals retinal vascular anatomy, consistent with electron micrograph.

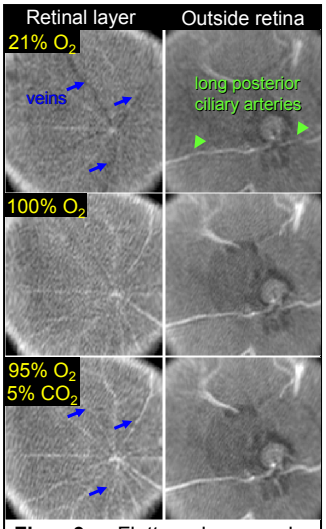

Fig 3. Flattened vascular structure at the retinal layer and tissue posterior to the retina. Vessels were enhanced during oxygen inhalation relative to air due to T_2* contrast. Further vascular enhancement was observed when breathing carbogen (95%O_2 + 5%CO_2) due to vasodilation.

REFERENCE [1] Cheng et al., *PNAS* 2006, 103:17525. [2] Blacharski, *Arch Opthalmol* 1985, 103:1301. [3] Ninomiya et al., *Vet Ophthalmol* 2001, 4:55. [4] Dollery et al., *IOVS* 1969, 8:588. [5] Wang et al., *Exp Eye Res* 2008, 86:908.