High resolution ΔR_2, ΔR_2*, and vessel density MRI of the rat ocular circulation

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INTRODUCTION The retina is nourished by two distinct circulations. The *retinal circulation* is on the inner retinal surface and projects into the ganglion cell layer, inner plexiform layer and inner nuclear layer. The *choroid circulation*, sandwiched between the retinal pigment epithelium and sclera, supplies the *avascular* outer nuclear and photoreceptor layers [1]. The unique anatomical structure of the retina provides a great opportunity to investigate the intra- and extravascular component of the MRI signals. However, the ΔR_2 (sensitive to microvessels) and ΔR_2* (sensitive to vessels of all sizes) [2,3] of the retinal and choroidal circulation as well as their extravascular contribution (i.e., to the middle avascular layer of the retina) remain to be determined. This study employed very high resolution MRI (30x30 μm) to reveal the MION-induced ΔR_2 and ΔR_2* profiles across the retinal thickness by using a retina linearization technique at an 11.7 T scanner. Along with this, the vessel density index of the rat retina was also established. The MRI-based vessel density index could serve as an alternative method of postmortem fluorescence microscopy-based vessel density measurement that has been widely used to characterize retinal and choroidal vascular degeneration or neovascularization in disease states [4, 5].

METHODS Fifteen rats were anesthetized with α-chloralose (60 mg/kg first dose, maintained with 30 mg/kg/hr, i.v.), mechanically ventilated, paralyzed with pancuronium bromide (4 mg/kg first dose, 4 mg/kg/hr, i.v.). Monocrystalline iron oxide nanoparticle (MION, 30 mg Fe/kg, i.v.) was used for ΔR_2 and ΔR_2* measurement. A custom-made small circular surface coil (ID~7 mm) was placed on the left eye. Magnetic field homogeneity was optimized using standard FASTMAP shimming with first order shims on an isotropic voxel of 7x7x7 mm, encompassing the entire eye. Scout images were acquired to plan a single mid-sagittal slice bisecting the center of the eye and optic nerve for subsequent imaging in order to minimize partial volume effect due to the retinal curvature [1]. High resolution gradient-echo (GE) MRI was measured using spectral width = 28 kHz, TR = 150 ms, TE = 5 ms, FOV = 7.7x7.7 mm, slice thickness = 1 mm, acquisition matrix = 256x128 (zero-filled to 256x256), yielding a nominal in-plane resolution = 30×30 μm. Spin-echo (SE) MRI parameters were essentially identical, except spectral width = 50 kHz, TR = 2000 ms, effective TE = 23 ms, echo train length = 8. Images were acquired in time series and corrected for motion and drift before additional analysis as needed. Quantitative analysis employed linearized profiles of the retina to minimize bias [1]. The vessel size index was defined as $\Delta R_2/(\Delta R_2^*)^{2/3}$, which should closely correlate with the histologic vessel density [6]. Statistical analysis was performed by paired t-tests.

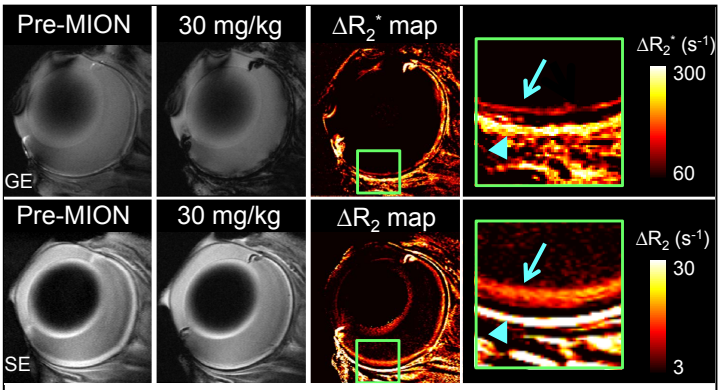

Fig 1. Layer-specific MION MRI of a rat eye. Gradient-echo and spin-echo MR images were acquired before and after 30 mg Fe/kg MION in the same rat. ΔR_2 and ΔR_2* maps were calculated and taken as blood volume indices. The arrows and arrowheads indicate the retinal (inner) and the choroidal (outer) circulation, respectively.

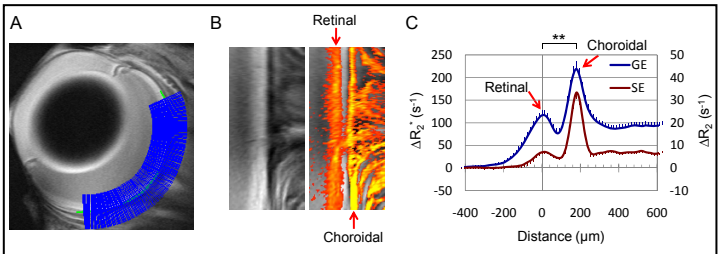

Fig 2. (A) The profiles (blue lines) were radially projected for linearizing the retina. **(B)** Linearized basal ΔR_2 map was color-coded and overlaid on a linearized spin-echo image, where the retinal and choroidal vascular layers were distinctly resolved. **(C)** ΔR_2^* (GE) and ΔR_2 (SE) profiles (mean ± SEM, n = 15) were obtained across the retinal thickness by averaging the signals along the retina. **p < 0.01.

RESULTS & DISCUSSION This study demonstrates high resolution ΔR_2 and ΔR_2^* profiles to MION injection of the rat retina. The major findings are: (i) The ΔR_2 map, with 180º refocusing RF pulses, showed a better-resolved vascular structure of the eye. (ii) The ΔR_2 and ΔR_2^* ratios of choroid to retinal peak were 4.79 and 1.88, respectively. (iii) The ΔR_2^* profile at the middle avascular layer did not return to the baseline, indicating a stronger extravascular effect of MION in GE MRI compared to SE. (iv) The vessel density index, defined via $\Delta R_2/(\Delta R_2^*)^{2/3}$, was higher in the choroid than that in the retinal vascular layer, which was in good accordance with the *ex vivo* findings using electron microscopy [7]. In addition, our finding is in qualitative agreement with an earlier MRI study in rats utilizing Gd-DTPA, in which the subtraction of post and pre contrast images showed the choroid vascular layer to be significantly more enhanced than the retinal vascular layer, although no quantitative analysis was performed [1]. Furthermore, the vessel density indices derived from the ΔR_2 and ΔR_2* relationship, could have practical application in noninvasive, longitudinal study of retinal and choroidal vascular degeneration or neovascularization.

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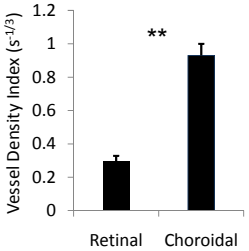

Fig 3. Vessel density indices of the retinal and the choroidal vascular layer (n = 15). The vessel size indices of the two vascular layers were estimated from the profile peak values in Fig 2C. The choroid has significant higher vessel density than the retinal vasculature (p<0.01).