Layer-Specific Blood-Flow MRI of Retina Degeneration at 11.7T

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Background: Retinitis pigmentosa (RP) is a family of inherited retinal diseases. The Royal College of Surgeons (RCS) rat [1] is an established animal model of RP with a mutation in the Mertk gene. This mutation leads to impaired phagocytosis of the photoreceptor segments, resulting in spontaneous photoreceptor degeneration similar to human patients with RP. The retina degeneration begins around 20 day after birth (P20) and complete by P90 [2].

Blood flow (BF) to the retina is supplied by two separate circulations, the retinal and choroidal vasculatures. Retinal BF (RBF) and choroidal BF (ChBF) may be altered in retinal diseases including RP and their response to the diseases may be different. Thus the ability to image laminar specific BF could have important applications for staging diseases and monitoring novel therapeutic interventions. In contrast to optical imaging techniques, MRI has the unique advantage of providing depth-resolved and quantitative BF data with a large field of view. Advances in MRI technologies have allowed very high spatial resolution capable of laminar resolution in the thin retina.

We previously developed high-resolution, layer-specific BF MRI to image quantitative RBF and ChBF at 11.7T with 44x44x600 μm^3 resolution, and as a demonstration of feasibility showed reduced RBF and unaffected ChBF at the end stage of retina degeneration in a small number of RCS rats compared to normal controls [3]. In this study we expand upon our previous findings by imaging at earlier time points to observe the longitudinal progression of BF changes due to retinal degeneration.

Method: RCS rats (n = 3, 5, 5 at postnatal day P40, P60, P90-120) and age-matched, normal Long Evans rats used as controls (n = 4, 5, 6, about postnatal day P40, P60, P90-110) were anesthetized under ~1% isoflurane, mechanically ventilated, and paralyzed using pancuronium bromide. Physiology parameters including end-tidal CO2, O2 saturation, heart rate and rectal temperature were maintained within normal ranges. MRI was performed on a 11.7 T/16 cm Bruker scanner with a 75 G/cm gradient and a small surface eye coil with active decoupling for imaging (ID=1 cm for P60 and P90, ID=0.7 cm for P40) and a butterfly neck coil for arterial spin labeling placed at the neck. BF MRI of a single axial slice bisecting the optic nerve was acquired using arterial-spin labeling and gradient-echo inversion-recovery EPI with 10x10 mm FOV, 2.1 s labeling pulse, 4.0s TR per segment, 2.1s TI (which occurred during labeling duration), 228x228 matrix zero-padded to 256x256, single 0.6 mm slice, 6 segments, and 15.4 ms TE. Typically, 20 pairs (labeled and non-labeled) of images were acquired for averaging. BF profiles across the retinal thickness were obtained [4].

Results: Figure 1A shows a representative BF image of a normal rat eye. RBF and ChBF layers and the avascular layer in between are well resolved. Figure 1B, 1C and 1D show the group-averaged BF profiles across the retinal thickness at P40, P60 and P90. BF profiles of the normal retinas show two well-resolved peaks corresponding to retinal and choroidal vascular layers, while the BF profiles of the RCS retinas showed only one choroidal peak at P60 and P90. At P40, BF profiles of RCS rats still show two well resolved peaks, just like normal controls. ChBF was unchanged in RCS rats. Figure 2 summarize the BF values.

Discussion & Conclusion: This study demonstrated layer-specific quantitative BF changes in the retina during progressive retinal degeneration in rats at 11.7T. The ChBF are similar between RCS and control rats at all three time points. However, at P60 and P90, RCS groups do not show the retinal peak in the BF profiles, while the corresponding normal BF profiles show well resolved retinal peak. On the other hand, at P40, both RCS and normal group show well resolved RBF peak in their BF profiles and their BF measurement are not considerably different. In our previous report [3], histological thickness of the retina confirmed atrophy of the outer nuclear layer (ONL) and the photoreceptor segments at end point (P90). The total retinal thickness, excluding the choroid, was 191±3μm for controls and 105±18 μm for RCS rat retinas after P90. Together these data indicate: 1) ChBF likely does not respond to atrophy of ONL and photoreceptor segments. 2) The retinal vascular layer may not be significantly damaged at P40, but after P60, it may be seriously damaged. The retinal vascular layer may also be closer to the choroid, due to thinning of the outer retina, so that the two layers can't be resolved with 44 μm in-plane resolution. We believe both situations, damage of retinal vasculature and reduced separation of the two vascular layers, happen.

Our findings are supported by: 1) Nilsson et al [6] who reported RBF was severely decreased but ChBF is not significantly affected in a cat model of retinal degeneration using destructive microspheres BF measurement. 2) Wang et al [7] who reported detection of vascular damage in retinal circulation of RCS rat retinas despite the inner retina appearing relatively intact in histology.

In conclusion, choroidal and retinal circulations are affected differently by retinal degeneration. BF MRI offers the ability to image RBF and ChBF quantitatively without depth limitation. It also has potential to provide layer-specific multimodality anatomical, physiological and functional) information in the same setting. This approach could open up new avenues for retinal disease research.

References 1) Gal et al, Nat Genet 2000 , 26:270. 2) Dowling et al, J. Cell Biol 1962; 14: 73–109. 3) Li et al., ISMRM 2010. 4) Li et al. IOVS 2009, 50:1824. 5) Cheng et al., PNAS 2006, 103:17525. 6) Nilsson et al., IOVS 2001 42:1038. 7) Wang et al, Curr Eye Res 2003, 27:183.

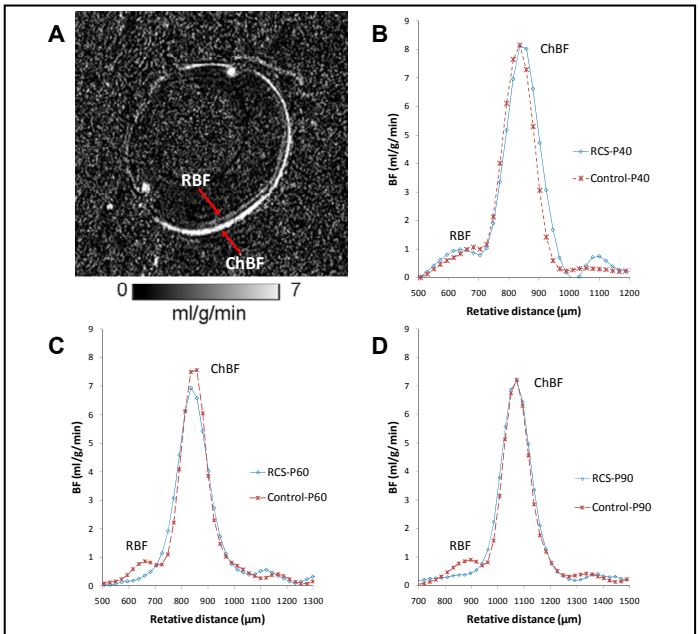

Figure 1. (A) BF MRI of the retina at 44x44x600 μm^3 from a single normal animal. (B), (C) and (D) Group-averaged BF profiles across the retinal thickness for normal and RCS rat retinas at postnatal day 40, 60, and 90~120.

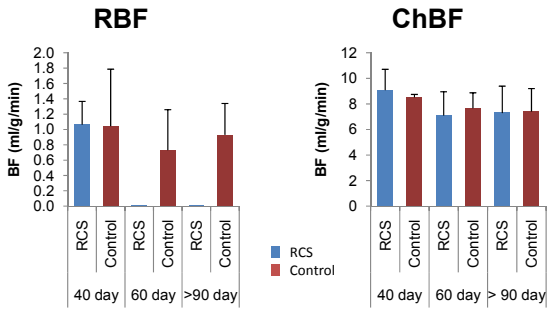

Figure 2 Mean RBF and chBF peak values (error bars: standard deviation)